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Medizinische Klinik II, Nephrologie und Nierentransplantation

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Aktuelle Herausforderungen bei der Behandlung chronisch niereninsuffizienter Patienten

- neurokognitive und immunologische Aspekte -

Habilitationsschrift

zur Erlangung der Lehrbefähigung für das Fach

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Die folgende kumulative Habilitationsschrift setzt sich mit neurokognitiven und immunologischen Aspekten sowie deren klinischer Relevanz bei niereninsuffizienten Patienten auseinander. Ihr liegen 7 Originalarbeiten zugrunde, die sich im Einzelnen befasst haben mit:

1. der Erfassung der kognitiven Beeinträchtigung und der damit verbundenen Risikofaktoren bei Hämodialysepatienten

Karakizlis H, Bohl K, Ziemek J, Dodel R, Hoyer J. *Assessment of cognitive impairment and related risk factors in hemodialysis patients.* J Nephrol. 2022; 35(3):931-942.

2. dem Einfluss des Zeitpunktes von neurokognitiven Testungen bei Dialysepatienten

Karakizlis H, Thiele S, Greene B, Hoyer J. *Cognitive performance in dialysis patients - "when is the right time to test?".* BMC Nephrol. 2021;22(1):205.

3. möglichen Risikofaktoren und Behandlungsansätzen von kognitiven Beeinträchtigungen bei Patienten vor und nach Nierentransplantation

Karakizlis H, Doerr JM, Becker A, Nahrgang C, Rainer L, Askevold I, et al. *Neuropsychological Assessment of Cognitive Impairment in Kidney Transplantation (NAsKiT) and its related risk factors: a study protocol.* J Nephrol. 2022;35(7):1933-1941.

4. der potenziellen Möglichkeit, bereits transplantierte Organe nach Versterben des Empfängers erneut zu transplantieren

Karakizlis H, van Rosmalen M, Boide P, Askevold I, Vogelaar S, Lorf T, et al. *Retransplanting a previously transplanted kidney: A safe strategy in times of organ shortage?* Clin Transplant. 2022;36(3):e14554.

5. dem ELISpot-Assay zur Beurteilung der Immunogenität und Reaktogenität nach mRNA-basierter Impfung bei Dialysepatienten

Karakizlis H, Nahrgang C, Strecker K, Chen J, Aly M, Slanina H, et al. *Data on immunogenicity and reactogenicity to COVID-19 vaccination among patients receiving maintenance dialysis.* Data Brief. 2022; 42(16):108271.

6. der Beurteilung der Immunogenität und Reaktogenität homologer mRNA-basierter und vektorbasierter SARS-CoV-2-Impfstoffregime bei Dialysepatienten nach Grundimmunisierung

Karakizlis H, Nahrgang C, Strecker K, Chen J, Aly M, Slanina H, et al. *Immunogenicity and reactogenicity of homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimens in patients receiving maintenance dialysis*. Clin Immunol. 2022;236:108961.

7. der humoralen und zellulären Immunreaktionen auf die mRNA-1273-SARS-CoV-2-Booster-Impfung bei Dialysepatienten

Karakizlis H, Agarwal V, Aly M, Strecker K, Csala B, Esso I, et al. *Humoral and cellular immune responses to the mRNA-1273 SARS-CoV-2 vaccine booster in patients on maintenance dialysis.* J Nephrol. 2022;22:1–4. Epub ahead of print.

Die nachfolgende Darstellung skizziert die Hintergründe und Zielsetzungen dieser Arbeit (Kapitel 1, Einleitung), diskutiert ihre wesentlichen Ergebnisse (Kapitel 2, Diskussion) und gibt einen Ausblick auf zukünftige Forschungsfragen (Kapitel 3, Zusammenfassung und Ausblick). Kapitel 4 enthält die jeweiligen Originalpublikationen.

INHALTSVERZEICHNIS

1. EINLEITUNG

Eine chronische Niereninsuffizienz (CKD) liegt vor, bei einem Funktionsverlust der Niere mit einer glomerulären Filtrationsrate (GFR) <60ml/min mit oder ohne Auftreten einer Proteinurie. Dieser Zustand muss länger als 3 Monate vorliegen und sich auch auf den Gesundheitszustand auswirken[1]. Bei 9–14 % der Weltbevölkerung ist eine CKD zu beobachten[2]. Die CKD wird in 5 Stadien eingeteilt (CKD 1–5), wobei das Stadium CKD 5 einer terminalen Niereninsuffizienz entspricht und die Patienten eine Nierenersatztherapie benötigen, welche aus einer Peritonealdialyse, Hämodialyse oder einer Nierentransplantation bestehen kann. Laut dem IQTIG-Jahresbericht 2019 des gemeinsamen Bundesausschusses[3] erhalten derzeit in Deutschland 93089 Menschen eine Dialysetherapie. Dies entspricht mehr als einer Verdoppelung der Fälle innerhalb der letzten 20 Jahre. Insgesamt sind ca. 25000 ursprüngliche Dialysepatienten nierentransplantiert worden, somit gibt es in Deutschland mehr als 110000 terminal niereninsuffiziente Patienten, was einer Prävalenz von ca. 0,1 % entspricht[4].

Durch die demografische Entwicklung und der damit verbundenen Alterung der Bevölkerung in Deutschland ist aufgrund der zunehmenden Inzidenz der terminalen Niereninsuffizienz im höheren Alter von einer kontinuierlichen Zunahme von Patienten mit terminaler Niereninsuffizienz auszugehen. Diese Entwicklung hat auch erhebliche gesundheitsökonomische Auswirkungen, denn das Gesundheitssystem muss sich auf die spezifischen Erkrankungen und Behandlungsformen älterer Patienten einstellen, bei denen auch zunehmend mit der Einschränkung kognitiver Leistungsfähigkeit gerechnet werden muss.

Die Beeinträchtigungen der kognitiven Leistungsfähigkeit bei Patienten mit CKD sind in den vergangenen Jahren immer mehr in den Fokus gerückt und stellen eine wichtige Herausforderung in der Behandlung bei Patienten mit chronischer Niereninsuffizienz dar. Studien konnten zeigen, dass eine zunehmende Niereninsuffizienz zu einer vermehrten Beeinträchtigung der kognitiven Leistungsfähigkeit führt[5-8], welche insbesondere bei terminaler Niereninsuffizienz auf bis zu 80 % ansteigt[5].

Aufgrund der erhöhten Lebenserwartung und der Zunahme der Inzidenz der terminalen Niereninsuffizienz wird sich die Zahl der Patienten, welche auf eine Transplantation warten, weiter erhöhen und damit auch der Bedarf an Nierenorganen[9]. Bei gleichzeitig sinkenden Zahlen an zu transplantierenden Organen resultieren hieraus eine längere Wartezeit für Dialysepatienten auf der

Nierentransplantationswarteliste, ein damit verbundenes erhöhtes kardiovaskuläres Risiko und eine erhöhte Sterblichkeitsrate der Patienten[10,11]. Rana et al.[12] konnten in einer Analyse aus dem US-Datenregister nachweisen, dass in einem Zeitraum der letzten 25 Jahre mehr als 2 Millionen Lebensjahre durch Transplantationen von soliden Organen gerettet werden konnten. Besonders erwähnenswert ist die Tatsache, dass die Lebenserwartung nach einer Nierentransplantation signifikant ansteigt und dies in jeder Altersklasse nachzuweisen ist[13]. Die Herausforderung besteht aktuell darin, neue Wege zu finden, um den Pool an zu transplantierenden Organen zu erhöhen.

Die weltweite Pandemie der Coronavirus-2-Infektion inklusive des schweren akuten respiratorischen Syndroms (SARS-CoV-2) hat Nephrologen und andere Fachdisziplinen vor die Herausforderung gestellt, spezifische Therapien zu entwickeln, die aufgrund der neuen Variante des Coronavirus zu Beginn nicht verfügbar waren. Mittlerweile gibt es zwar zugelassene Impfstoffe, die bei der Normalbevölkerung zu einer robusten Impfantwort führen, es besteht jedoch weiterhin ein dringender Bedarf an mehr Daten über terminal niereninsuffiziente Patienten, da die Wirksamkeit der Impfstoffe in dieser Bevölkerungsgruppe nicht explizit getestet wurde[14,15]. Durch eine Ausweitung der Kenntnisse zur Immunantwort bei Patienten mit terminaler Niereninsuffizienz können die Impfprotokolle für diese Population bei Bedarf angepasst werden, um einen angemessenen antiviralen Schutz für diese gefährdete Bevölkerungsgruppe zu erreichen.

1.1. Chronische Niereninsuffizienz und kognitive Leistungsfähigkeit

Die Beeinträchtigung der kognitiven Leistungsfähigkeit in Verbindung mit Demenzerkrankungen ist ein globales Gesundheitsproblem, an dem weltweit etwa 50 Millionen Menschen leiden. Diese Zahl wird sich bis 2050 wahrscheinlich verdreifachen[16]. In Deutschland leiden ca. 1,2 Millionen Menschen an einer Demenz[17]. Sie stellt eine enorme wirtschaftliche und gesellschaftliche Belastung dar, so werden die wirtschaftlichen Kosten auf ca. 1,1 % des weltweiten Bruttoinlandsprodukts geschätzt[16].

Demenzerkrankungen bei älteren Menschen führen in ihrem Verlauf in aller Regel zur Unfähigkeit der eigenständigen Haushaltsführung und häufig zur Notwendigkeit häuslicher oder stationärer Pflege[18]. Die Prävalenzraten von Demenz sind stark

altersabhängig und steigen von 0,8 % bzw. 0,6 % im Alter von 60–64 Jahren für Männer und Frauen auf 30 % bzw. 43 % für über 100-jährige Männer und Frauen[17].

Unter kognitiven Funktionen versteht man die Hirnleistungsfunktionen verschiedener Domänen wie Gedächtnis (Lernen und Erinnern), Exekutivfunktion (z.B. Planen und begründetes Handeln), Aufmerksamkeit und Geschwindigkeit (Konzentration, Geschwindigkeit der Informationsaufnahme und -analyse), Wahrnehmung und Motorik (Verknüpfung visueller, taktiler oder auditiver Informationen mit motorischer Aktivität) sowie Sprache (Wortfindung, Sprachfluss). Erst durch die kognitiven Funktionen ist es uns möglich, ein zeitlich geordnetes und inhaltlich kohärentes Bild von unserer Umwelt und von uns selbst zu erstellen[19].

Defizite in einer oder mehreren dieser Domänen sind definiert als kognitive Beeinträchtigung[20] und sie liegen vor, wenn die kognitive Leistungsfähigkeit um mehr als das 1,5-fache der Standardabweichung von dem normativen Mittelwert (alters- und bildungskorrigiert) abweicht oder die Aktivitäten des täglichen Lebens beeinträchtigt[16]. Kognitive Beeinträchtigungen können von leichten bis zu schweren Formen reichen, wobei schwere Beeinträchtigungen, die das tägliche Leben und die Unabhängigkeit einschränken, typischerweise als Demenz bezeichnet werden[21]. Es wird davon ausgegangen, dass bei 20 % der Patienten mit einer milden kognitiven Störung innerhalb eines Jahres[22] bzw. bei 50 % in 5 Jahren[19] ein Progress zu einer manifesten Demenz erfolgt. Demenzerkrankungen sind definiert durch den Abbau und Verlust kognitiver Funktionen und Alltagskompetenzen. Bei den zumeist progressiven Verläufen kommt es u.a. zu Beeinträchtigungen der zeitlich-örtlichen Orientierung, der Kommunikationsfähigkeit, der autobiografischen Identität und von Persönlichkeitsmerkmalen. Häufig ist das schwere Stadium der Demenz durch vollständige Hilflosigkeit und Abhängigkeit von der Umwelt charakterisiert[23].

Die milde kognitive Störung gewinnt in der klinischen Forschung zunehmend an Bedeutung, da in dieser Phase Veränderungen der kognitiven Leistungsfähigkeit mit großer zeitlicher Dynamik ablaufen und hier noch eine Progressionsminderung erreicht werden könnte[24].

Obwohl die CKD gemeinhin nicht als wichtiger Risikofaktor für Demenz anerkannt wird, gibt es einen starken Zusammenhang zwischen CKD und kognitiver Beeinträchtigung[5,16,25]. Bereits ab einer glomerulären Filtrationsrate (GFR) von < 60 ml/min/1,73 m^2 oder dem Vorhandensein einer Albuminurie mit einem Albumin-Kreatinin-Quotient von > 30mg/g besteht im Vergleich zur Allgemeinbevölkerung ein

wesentlich höheres Risiko für kognitive Beeinträchtigungen. Die Prävalenz kognitiver Beeinträchtigungen bei CKD-Patienten beträgt je nach CKD-Stadium und Methode zur Bewertung der kognitiven Beeinträchtigung 10 % bis 80 %[5,20,26,27].

Da nierenkranke Menschen häufig mehrere Begleiterkrankungen haben, ist es nicht überraschend, dass die Ursache für kognitive Beeinträchtigungen bei CKD-Patienten multifaktoriell ist. Traditionelle kardiovaskuläre Risikofaktoren, wie Alter, Bluthochdurck, Dyslipidämie und Diabetes mellitus spielen hierbei genauso eine wichtige Rolle wie nierenassoziierte (z.B. Urämie und Anämie) und dialyseassoziierte (Hypotension und reduzierte zerebrale Perfusion) Ursachen.

Wichtig ist, dass viele CKD-Patienten älter sind und daher ein Risiko für die Entwicklung einer Alzheimer-Demenz haben, die in ihren frühen Stadien vor allem das Gedächtnis beeinträchtigt. Die Häufigkeit von Alzheimer-Demenz bei CKD-Patienten scheint jedoch ähnlich zu sein wie bei Patienten ohne Nierenerkrankung in ähnlichem Alter und mit ähnlicher Belastung durch Begleiterkrankungen, was darauf hindeutet, dass die Alzheimer-Demenz nicht der vorherrschende oder primäre Grund für das erhöhte Risiko bei Patienten mit CKD ist[28].

Im Gegensatz dazu haben Patienten mit einer CKD ein deutlich höheres Risiko, an zerebrovaskulären Erkrankungen, insbesondere der kleinen Gefäße, zu erkranken, was darauf hinweist, dass dies ein wichtiger Faktor für die Entwicklung von CKD-bedingten kognitiven Beeinträchtigungen sein könnte[20]. Für diese Hypothese gibt es mehrere Anhaltspunkte. Erstens haben Menschen mit CKD eine hohe Prävalenz von kardiovaskulären Erkrankungen (CVD) und CVD-Risikofaktoren, einschließlich Diabetes, Bluthochdruck und Dyslipidämie, die oft so schwerwiegend sind, dass sie zu einer chronischen Niereninsuffizienz führen[29,30]. Zweitens haben Menschen mit CKD häufiger klinische zerebrovaskuläre Erkrankungen, einschließlich Schlaganfall und transitorischer ischämischer Attacke, sowie subklinische zerebrovaskuläre Erkrankungen in der MRT-Bildgebung[31,32]. Drittens betreffen die mit zerebrovaskulären Erkrankungen verbundenen kognitiven Defizite vor allem die Verarbeitungs- und Exekutivfunktionen, also kognitive Bereiche, die sich auf die Planung und Durchführung von Aufgaben auswirken, welche bei Personen mit CKD am stärksten betroffen sind[5,27,33]. Viertens werden chronisch vaskuläre Erkrankungen und ihre Risikofaktoren mit einer schlechteren exekutiven Funktion in Verbindung gebracht[33]. Darüber hinaus wird in früheren Stadien der CKD das Vorhandensein einer Albuminurie, die wahrscheinlich für eine systemische Gefäßschädigung steht, mit einer

schlechteren exekutiven Funktion und dem Auftreten einer Demenz in Verbindung gebracht[28,34-36].

1.2. NIERENTRANSPLANTATION UND ORGANMANGEL

Ende 2021 warteten in Deutschland 6593 Patienten[37] aktiv auf eine Nierentransplantation, in der gesamten Eurotransplant-Region standen 10269 Patienten[38] auf der aktiven Warteliste. Demgegenüber wurden im Jahr 2021 in Deutschland nur 1517[37] und in der gesamten Eurotransplant-Region nur 2959 Nieren transplantiert[38]. Das sind 517 bzw. 720 Organe weniger als noch im Jahr 2010[39]. Die Wartezeit auf eine Nierentransplantation durch einen verstorbenen Spender beträgt in Deutschland in der Regel 6–8 Jahre[37] und in der Eurotransplant-Region etwa 4 Jahre[38]. Durch die lange Wartezeit auf der Transplantationsliste erhöht sich das kardiovaskuläre Risiko und damit auch die Sterblichkeitsrate der Patienten[10,11]. Auch der demografische Wandel, die Alterung der Bevölkerung verbunden mit einer erhöhten Inzidenz für eine terminale Niereninsuffizienz und andere Organversagen[9] sowie der Rückgang der Zahlen transplantierter Organe Deutschland haben das Problem in den vergangenen Jahren noch verschärft.

Politisch ist 2019 das „Gesetz zur Verbesserung der Zusammenarbeit und der Strukturen bei der Organspende“ erlassen worden, welches insbesondere an den zuvor identifizierten Schwachstellen ansetzt. Zum einen sollen die Bedingungen und Abläufe für die Organspende in den Entnahmekliniken sowie bei der Erkennung möglicher Spender verbessert werden. Das neue Gesetz stärkt die Rolle der derzeit mehr als 1 400 Transplantationsbeauftragten in deutschen Kliniken und sorgt für eine aufwandsgerechte Vergütung der Entnahmekrankenhäuser für ihre Leistungen im Zusammenhang mit der Organspende[40]. 2018 beauftragten der Spitzenverband der Gesetzlichen Krankenkassen, die Bundesärztekammer und die Deutsche Krankenhausgesellschaft die Gesundheitsforen Leipzig mit dem Aufbau und Betrieb des deutschen Tx-Registers welches seit Juli 2021 seine Arbeit aufgenommen hat. Hierdurch werden in Deutschland erstmalig medizinisch relevante und bislang dezentral gewonnene Daten von verstorbenen Organspendern, Organempfängern und Lebendspendern zentral zusammengefasst und miteinander verknüpft [41].

Des Weiteren wurden bereits neue Optionen der Nierenspende realisiert, z.B. die Nierenlebendtransplantation über ABO- oder HLA-inkompatible Barrieren[42-46],

Nierentauschprogramme für die Lebendtransplantation (Cross-Over)[43,47] und die Erweiterung des Pools verstorbener Spender durch verstärkte Nutzung sogenannter marginaler Spender, wie im Rahmen des Eurotransplant-Senior-Programms[9,48], die Doppelnierentransplantation[49] oder auch die Verwendung von Nieren mit schwerem akutem Nierenversagen[50,51] und Transplantation von Organen Hepatitis C positiver Spender[52]. Derzeit haben all diese Maßnahmen jedoch nicht zu einem Anstieg der Nierentransplantationszahlen geführt.

1.3. Chronische Niereninsuffizienz und SARS-CoV-2

Das Jahr 2020 war für die Gesellschaft und die Gesundheitssysteme weltweit eine Herausforderung, erkennbar daran, dass die Coronavirus-19-Krankheit (COVID-19) von der WHO im März 2020 zur Pandemie erklärt wurde. COVID-19 hat weltweit Millionen von Todesfällen verursacht und ist besonders tödlich für gefährdete Bevölkerungsgruppen wie Patienten mit chronischer Niereninsuffizienz, Dialysepatienten und nierentransplantierte Patienten[53,54]. Dialyse, Organtransplantation und eine chronische Niereninsuffizienz in Stadium 4 (eGFR < 30 ml/min/1,73 m^2) sind 3 der 4 Komorbiditäten, die mit dem höchsten Mortalitätsrisiko durch COVID-19 verbunden sind[55]. Mehrere Umstände haben die Auswirkungen von SARS-CoV-2 auf die Morbidität und Mortalität von CKD-Patienten verschärft. Abgesehen von der inhärenten Immunsuppression infolge der eingeschränkten Nierenfunktion[56] weisen Dialyse- und nierentransplantierte Patienten spezifische Merkmale auf, die ihr Risiko für die Entwicklung einer schweren COVID-19 Erkrankung erhöhen, z.B. eine zusätzliche immunsuppressive Therapie bei Nierentransplantierten.

Nachdem sich auch 10 Monate nach dem Ausbruch noch keine spezifische Behandlung für schwere Formen von COVID-19 durchgesetzt hatte, gelang es durch die Einführung der von der Europäischen Arzneimittelagentur (EMA) zugelassenen Impfstoffe (2 mRNA-basierte COVID-19-Impfstoffe (mRNA-1273 [Moderna Biotech] und BNT162b2 [Pfizer-BioNTech]) und 2 vektorbasierte Impfstoffe (ChAdOx1 nCoV-19 [Oxford-AstraZeneca]; Ad26.COV2.S [Johnson & Johnson-Janssen])[57]), insbesondere in Ländern mit hoher Impfrate[53] vor schweren Verläufen der SARS-CoV-2-Erkrankung zu schützen[58,59]. Diese Impfstoffe lösen bei gesunden Personen robuste humorale und zelluläre Immunantworten gegen das Spike-Protein des SARS-CoV-2 aus. Es ist jedoch nicht bekannt, ob die Ergebnisse auch für Patienten mit chronischer

Niereninsuffizienz verallgemeinert werden können, weil die Wirksamkeit der Impfstoffe in dieser Bevölkerungsgruppe nicht explizit getestet wurde, da sie von den SARS-CoV-2-Impfstudien ausgeschlossen wurden[14,15]. Die bisher vorliegenden begrenzten Daten deuten auf eine verminderte Impfstoffreaktion bei Patienten mit terminaler Niereninsuffizienz hin[60,61], wobei es jedoch keine gesicherten Daten zur zellulären Immunität gibt.

1.4. Synopsis der Ziele eigener Untersuchungen

Vor dem Hintergrund der aktuellen Bevölkerungsstruktur sowie der prognostizierten Entwicklung mit einer Zunahme älterer Patienten mit chronischer Niereninsuffizienz beschäftigt sich die vorliegende Arbeit mit den aktuellen Herausforderungen in der Behandlung der chronischen Niereninsuffizienz. Berücksichtigt werden hier vor allem neurokognitive und immunologische Aspekte eigener klinischer Arbeiten.

Es ist bekannt, dass Patienten mit einer terminalen Niereninsuffizienz ein erhöhtes Risiko für kognitive Beeinträchtigungen haben[5,25,62]. Kognitive Beeinträchtigungen bedeuten wahrscheinlich einen hohen individuellen Verlust an Lebensqualität, eine frühzeitige Einschränkung der Selbstbestimmung und der Therapietreue, die für die Behandlung sehr wichtig ist. Die Früherkennung ist von größter Bedeutung, um präventive Maßnahmen zu ergreifen, krankheitsbedingte Trauer zu bewältigen und Missverständnisse bei der medizinischen Versorgung zu vermeiden[25]. In vielen der publizierten Studien wurde als Test zur Messung der kognitiven Leistungsfähigkeit der Mini-Mental-Status-Test (MMST)[63] eingesetzt, welcher als Screening-Instrument konzipiert ist, jedoch nicht als Diagnoseinstrument verwendet wird. Dieser konzentriert sich auf Orientierung, Gedächtnis und Sprache. Er ist nicht gut geeignet, um verschiedene krankheitsbedingte kognitive Beeinträchtigungen zu erkennen. Diese erfordern die Durchführung von detaillierten neurokognitiven Testbatterien, sind jedoch oft zeitaufwändig und erfordern unterschiedliche Normen für jede Aufgabe und werden daher nicht als Screeningverfahren angewandt.

Ziel in unserer klinischen Studie war es, das Ausmaß der kognitiven Beeinträchtigung zu untersuchen und ein eindeutiges Profil der kognitiven Funktion bei Hämodialysepatienten zu erstellen. Deswegen haben wir zusätzlich zum Screeningtest noch ein Standardinstrument zur neuropsychologischen Beurteilung, das Consortium to Establish a Registry for Alzheimer's Disease (CERAD), bei Patienten mit leichter kognitiver Beeinträchtigung (MMST ≥ 24 Punkte) angewandt.

Außerdem untersuchten wir eine Reihe von Risikofaktoren für Defizite in der kognitiven Leistungsfähigkeit sowie für deren zeitliche Entwicklung (A1)[64].

Da Hämodialysepatienten während der Dialyse akuten hämodynamischen Veränderungen und großen Flüssigkeitsverschiebungen ausgesetzt sind, ist eine intradialytische Hypotonie bei ihnen ein häufiges Phänomen und tritt bei über 30 % der Patienten auf. Sie ist nicht nur mit einer erhöhten Sterblichkeit verbunden[65], sondern scheint sich auch auf die kognitive Leistungsfähigkeit von Dialysepatienten durch Veränderung des zerebralen Blutflusses auszuwirken[26,66]. Ein niedriger diastolischer Blutdruck bei älteren Menschen wird außerdem zusätzlich mit einem erhöhten Risiko für die Entwicklung einer Demenz in Verbindung gebracht[67]. Somit stellte sich uns die Frage, ob der Zeitpunkt der neurokognitiven Testung einen Einfluss auf die kognitive Leistungsfähigkeit in unserem Dialysekollektiv hat. Dies ist insbesondere deshalb von klinischem Interesse, da eine potenzielle Verschlechterung der kognitiven Leistungsfähigkeit an der Dialyse zu einer Beeinträchtigung der Patientenadhärenz führen könnte, sodass Medikationspläne nicht verstanden werden, wenn die Arzt-Patienten-Kommunikation während der Dialyse stattfindet. Für diese Testungen führten wir die neurokognitiven Untersuchungen an 3 verschiedenen Zeitpunkten (innerhalb der ersten 90 Minuten, der letzten 90 Minuten einer Dialysetherapie sowie am dialysefreien Tag) durch (A2)[68].

Da bekannt ist, dass die Zunahme der chronischen Niereninsuffizienz zu einer Verschlechterung der kognitiven Leistungsfähigkeit führt[64,69], stellte sich die Frage, ob dieser Effekt auch umkehrbar ist (ob also eine Verbesserung der kognitiven Leistungsfähigkeit durch Verbesserung der Nierenfunktion erreicht werden kann). Die beste Möglichkeit, dies zu untersuchen, ist nach einer Nierentransplantation, die zu einer signifikanten Verbesserung der Nierenfunktion führt. Einige wenige Daten zeigen, dass Nierentransplantierte zwar eine schlechtere kognitive Leistungsfähigkeit als die Normalbevölkerung aufweisen[70,71] und auch von einer erhöhten Sterblichkeit betroffen sind[72,73], die kognitive Funktion jedoch besser zu sein scheint als bei Dialysepatienten[74]. Die tatsächliche Prävalenz kognitiver Beeinträchtigungen bei Patienten nach einer Nierentransplantation (postmortal und lebend) ist jedoch unbekannt. Die Entwicklung der kognitiven Funktionen und das genaue Ausmaß (d.h., welche kognitiven Bereiche besonders betroffen sind) sind bei nierentransplantierten Personen noch nicht gut untersucht worden. Eine bessere Kenntnis der Prävalenz kognitiver Beeinträchtigung sowie des Verlaufs und des kognitiven Profils ist jedoch

wichtig für die Planung künftiger Studien, in denen die klinischen Auswirkungen kognitiver Beeinträchtigungen bewertet und Managementstrategien entwickelt werden können. Bislang gibt es nur eine begrenzte Anzahl von Studien, die sich auf die Auswirkungen einer Nierentransplantation auf die kognitiven Funktionen konzentrierten, wobei die Ergebnisse nicht einheitlich sind[75]. Wir planten daher eine Studie, die a) das Ausmaß der kognitiven Beeinträchtigung, b) den Verlauf der kognitiven Leistungsfähigkeit bei nierentransplantierten Personen und c) das Profil der kognitiven Beeinträchtigung untersucht (d.h., ob ein bestimmter kognitiver Bereich stärker betroffen ist als andere). Darüber hinaus werden die Auswirkungen und der zeitliche Verlauf von Variablen, die einen potenziellen Einfluss auf die kognitive Leistungsfähigkeit haben, untersucht. In diesem Zusammenhang interessierte uns außerdem ein möglicher Zusammenhang mit Depression, Stress (subjektiver Stress), und in diesem Rahmen langfristiger Aktivität der Hypothalamus-Hypophysen-Nebennieren-Achse (HHNA), weswegen diese Variablen für uns zusätzlich von besonderem Interesse sind (A3)[76].

Wie eingangs erwähnt, ist eine große Herausforderung der Transplantationsnephrologie, dem stetig wachsenden Organmangel entgegenzuwirken. Die Nierentransplantation ist nach wie vor die bevorzugte Therapie für Patienten mit terminaler Niereninsuffizienz. Sie wird jedoch durch den Mangel an Nierenspenden eingeschränkt. Trotz der Versuche, die Zahl der verstorbenen und lebenden Spender zu erhöhen, war der Erfolg bisher nur begrenzt. In Zeiten des Organmangels sollten neue Wege gefunden werden, um den Pool an verfügbaren Organen zu erweitern. Die Wiederverwendung einer transplantierten Niere könnte in unseren Augen ein solcher Ansatz sein. Da die häufigste Ursache für den Verlust eines Nierentransplantats der Tod des Patienten mit einem funktionierenden Transplantat ist (bis 25 %)[77-79], stellte sich die Frage, ob Organe, welche bereits einmal transplantiert wurden, erneut transplantiert werden können und dadurch der Pool an Nierenspendern vergrößert werden kann. Es gibt einzelne Fallberichte über bereits zuvor transplantierte Nieren, die erneut transplantiert wurden[80-85], aber die Frage, ob dieses Verfahren in Zeiten des Organmangels eine sichere Option darstellt oder ob für eine erfolgreiche Retransplantation einer bereits transplantierten Niere besondere Voraussetzungen – wie eine gute Nierenfunktion ohne einen längeren Zeitraum seit der vorherigen Transplantation – erfüllt sein sollten, ist bislang noch nicht beantwortet. Das Verstreichen eines langen Zeitraums seit der letzten Transplantation könnte mit erheblichen chronischen Veränderungen einhergehen, die sich möglicherweise nicht

im Serumkreatinin oder der eGFR des Spenders widerspiegeln, aber das Transplantationsergebnis nach einer weiteren Transplantation beeinträchtigen könnten. Daher führten wir eine systematische retrospektive Analyse in der Eurotransplant-Region durch, mit der Frage, ob die Retransplantation bereits transplantierter Nieren ein sicheres Verfahren darstellen könnte, um den Pool an Nierenspendern zu erhöhen (A4)[86].

Eine der aktuell größten Herausforderungen ist mit der seit 2020 bestehenden Coronavirus-19 Pandemie verbunden, in deren Rahmen schnell klar geworden ist, dass Patienten mit einer chronischer Niereninsuffizienz ein erhöhtes Mortalitätsrisiko haben. Die mittlerweile zur Verfügung stehenden gut wirksamen Impfstoffe sind oben beschrieben und führen bei der Normalbevölkerung zu einer robusten Impfantwort[14,15]. Es ist jedoch nicht bekannt, ob diese Ergebnisse auf Patienten mit CKD bzw. nach Nierentransplantation übertragbar sind, da die Wirksamkeit der Impfstoffe in dieser Bevölkerungsgruppe nicht explizit getestet wurde, da sie von den SARS-CoV-2-Impfstudien ausgeschlossen wurden[14,15]. Die bisher vorliegenden begrenzten Daten deuten auf eine verminderte Impfantwort bei Patienten mit terminaler Niereninsuffizienz hin[60,61]. Daher ist es dringend notwendig, die Anzahl von wissenschaftlichen Daten zu erhöhen, damit die Impfprotokolle bei Bedarf angepasst werden können, um einen angemessenen antiviralen Schutz für diese gefährdete Bevölkerungsgruppe zu erreichen. Das Hauptziel unserer Studien waren einerseits die Untersuchungen der humoralen und der zellulären Immunogenität und Reaktogenität eines homologen mRNA-basierten und eines vektorbasierten SARS-CoV-2-Impfschemas bei Dialysepatienten nach der Grundimmunisierung (A5 und A6)[87,88] und andererseits nach der Booster-Impfung 6 Monate nach Grundimmunisierung (A7)[89].

2. DISKUSSION

2.1. KOGNITIVE ASPEKTE DER CHRONISCHEN NIERENINSUFFIZIENZ

2.1.1. ERFASSUNG DER BEEINTRÄCHTIGUNG DER KOGNITIVEN LEISTUNGSFÄHIGKEIT UND DER DAMIT VERBUNDENEN RISIKOFAKTOREN BEI HÄMODIALYSEPATIENTEN

Zur Untersuchung der kognitiven Leistungsfähigkeit und zur Erstellung des kognitiven Profils bei Hämodialysepatienten wurde die umfassende neuropsychologische Testung, die sogenannte CERAD-Testbatterie, zu insgesamt 3 verschiedenen Zeitpunkten (Baseline, 3-Monats-Follow-up, 12-Monats-Follow-up) durchgeführt. Von insgesamt 479 in Frage kommenden Patienten absolvierten 408 Patienten alle Tests zu Studienbeginn (Baseline). Zusammenfassend zeigte sich, dass 14,0 % (n = 57), 36,5 % (n = 149) und 24,5 % (n = 100) der Patienten eine leichte, mittlere bzw. schwere Beeinträchtigung aufwiesen, sodass insgesamt ein sehr großer Anteil von 75 % (306 Patienten) von einer kognitiven Beeinträchtigung betroffen war. Lediglich 25 % (n = 102) der Patienten waren ohne kognitive Beeinträchtigung. Bei den Patienten mit einer kognitiven Beeinträchtigung waren alle kognitiven Bereiche tangiert, wobei Depressionen und ein niedriger Bildungsgrad einen negativen signifikanten Einfluss auf die Testergebnisse hatten. In den Follow-up-Untersuchungen nach 3 bzw. 12 Monaten wurde kein weiterer signifikanter Abfall der kognitiven Leistungsfähigkeit beobachtet (A1)[64].

Diese Ergebnisse stehen im Einklang mit früheren Studien, in denen eine Spanne von 30–80 % kognitiver Beeinträchtigungen festgestellt wurde[5,7,90-92]. Die kognitiven Leistungen in unserem Patientenkollektiv waren beim Kurzzeitgedächtnis, bei der phonematischen und semantischen Flüssigkeit am stärksten beeinträchtigt, am besten schnitten die Patienten indessen beim Benennen ab. Beeinträchtigungen bei verbalen Gedächtnistests wurden bereits früher bei Dialysepatienten festgestellt[65,67,93]. Ein Vergleich dieser Studien ist jedoch nicht einfach, da viele von ihnen die kognitive Leistungsfähigkeit mit dem MMST[63] geprüft haben, der das Ausmaß und das Fortschreiten der kognitiven Leistungsfähigkeit aufgrund seines Screening-Charakters möglicherweise unterschätzt.

Hämodialysepatienten weisen eine höhere Prävalenz traditioneller vaskulärer Risikofaktoren wie Bluthochdruck und Schlaganfall auf als die Bevölkerung ohne

CKD[94]. Gefäßerkrankungen sind bei ihnen eine wahrscheinlichere Ursache für kognitive Beeinträchtigungen als der Morbus Alzheimer[95]. Überraschenderweise unterschieden sich unsere Studienpopulationen (mit und ohne kognitives Defizit) nicht signifikant in Bezug auf die üblichen vaskulären Risikofaktoren. In der Literatur ist beschrieben, dass die kognitive Leistungsfähigkeit bei Patienten mit Auftreten von Bluthochdruck (systolisch erhöhter Blutdruck) signifikant abgenommen hat[96], was in unserer Population nicht nachgewiesen werden konnte. Begründet werden könnten die Unterschiede der Ergebnisse im Patientenkollektiv damit, dass in der Vergleichsstudie bei keinem Patienten eine Dialysetherapie durchgeführt wurde.Darüber hinaus unterschieden sich die Gruppen mit und ohne Schlaganfall/TIA nicht signifikant in der kognitiven Funktion. Ein Grund für dieses Phänomen könnte sein, dass Dialysepatienten eher zu stummen Hirninfarkten neigen[97]. Da diese ohne klinisches Korrelat eines fokal neurologischen Defizites auftreten (also subklinisch verlaufen), wird daher die Diagnose nicht bei allen Patienten gestellt.

Zusammenfassend lässt sich sagen, dass unsere Ergebnisse keine weiteren Anhaltspunkte für eine zugrundeliegende vaskuläre Pathologie als Hauptursache für kognitive Defizite liefern und stattdessen möglicherweise auf unbekannte Risikofaktoren für die Beeinträchtigung der kognitiven Leistungsfähigkeit bei Hämodialysepatienten hinweisen, die in dieser Studie nicht berücksichtigt wurden.

Wir haben auch detaillierte klinische Daten erhoben, um mögliche Risikofaktoren für Defizite in der kognitiven Leistungsfähigkeit zu ermitteln. Eine Studie zeigte, dass Dialysepatienten mit höheren Hämatokritwerten bessere Leistungen beim Arbeitsgedächtnis und der Aufmerksamkeit erbrachten als Patienten mit niedrigeren Hämatokritwerten[98]. Dies stimmt mit unseren Ergebnissen überein, die einen positiven Einfluss des Hämoglobinspiegels auf die Leistung im semantischen Fluss zeigten. Darüber hinaus fanden wir eine positive Wirkung von Nikotin auf die phonematische Geläufigkeit. Auch in der Literatur gibt es Belege für eine verstärkende Wirkung von Nikotin auf einige kognitive Funktionen wie das verbale Gedächtnis und die exekutiven Funktionen, dennoch bleibt Nikotinmissbrauch in anderer Hinsicht schädlich[99]. Ein niedrigeres Bildungsniveau wurde in unserer Studie in Übereinstimmung mit anderen Studien[100-102] mit einem kognitiven Abbau in Verbindung gebracht. Dies könnte durch die Assoziation eines niedrigeren Bildungsniveaus mit schlechten funktionellen und kognitiven Reserven erklärt werden.

Interessanterweise haben wir außerdem festgestellt, dass das Ausmaß des Rückgangs der kognitiven Leistungsfähigkeit zwischen den Gruppen unterschiedlich war und vom ursprünglichen kognitiven Niveau abhängig war. Nur Patienten, die bei Studienbeginn keine Beeinträchtigung aufwiesen, zeigten nach einem Jahr eine signifikante Verschlechterung der CERAD-Werte im Vergleich zum Studienbeginn, dies galt aber nicht für Patienten, die bereits bei Studienbeginn kognitiv beeinträchtigt waren. Eine mögliche Erklärung hierfür könnte ein sogenannter „Floor-Effekt“ sein, d.h., bei den bereits beeinträchtigten Patienten, waren die Werte so niedrig, dass eine weitere Verschlechterung nicht detektiert werden kann (eingeschränkte Varianz).

Depressionen bei Hämodialysepatienten sind einer der häufigsten psychologischen Aspekte bei Studien über Patienten mit Nierenversagen[103]. Um die Häufigkeit von Depressionen und ihre Auswirkungen auf die kognitiven Leistungen zu ermitteln, wurde die Geriatrische Depressionsskala (GDS) herangezogen; in unserer Studie waren Depressionen signifikant mit einem niedrigeren kognitiven Niveau verbunden. Auch andere Studien haben eine ähnliche Verschlechterung der kognitiven Leistungsfähigkeit bei Vorliegen einer Depression festgestellt[100,104,105]. Dies lässt sich auf die Auswirkungen der Depressionssymptome auf kognitive Bereiche wie exekutive Funktionen und Verarbeitungsgeschwindigkeit zurückführen[105].

Bemerkenswert ist die Tatsache, dass Depressionen bei Patienten mit chronischer Niereninsuffizienz häufig unterdiagnostiziert werden[106]. Die Schätzungen für die Prävalenz von klinischen Depressionen bei Patienten mit chronischer Niereninsuffizienz bis hin zur terminalen Niereninsuffizienz bewegen sich zwischen 20 % und 40 %[103,106], wobei die Diagnose einer Depression häufig nicht in der Diagnoseliste zu finden ist. In unserem Kollektiv wiesen nur 3,9 % der nicht beeinträchtigten Patienten die Kriterien einer Depression auf, während 9,8 % (leichte kognitive Beeinträchtigung) bzw. 10 % (schwere kognitive Beeinträchtigung) die Kriterien für eine Depression erfüllten. Im Vergleich zur Häufigkeit einer kognitiven Beeinträchtigung scheint nur ein geringer Prozentsatz unserer Patienten an Depressionen zu leiden. Eine mögliche Erklärung könnte die Verwendung unterschiedlicher Methoden zur Diagnose von Depressionen in den jeweiligen Studien sein. In unserer Studie haben wir dazu den GDS als kurzes und kostengünstiges Instrument zur Messung depressiver Symptome bei älteren Erwachsenen herangezogen. Der GDS ist jedoch Screening-Instrument, sodass die Anwendung umfassenderer Depressionsskalen wie des Beck-Depressions-Inventars (BDI) oder

der Montgomery-Åsberg Depression Rating Scale (MADRS) zu anderen Ergebnissen führen könnte und und ggf. mehr Patienten eine Depression aufweisen könnten.

2.1.2. Der Einfluss des Zeitpunktes der neurokognitiven Testung bei Dialysepatienten

Einige Studien, die die kognitive Leistungsfähigkeit bei Dialysepatienten untersucht haben, berichteten von einem Zeittesteffekt mit optimaler Funktion 24 Stunden nach der Dialyse und von einer Verschlechterung der kognitiven Leistungsfähigkeit während oder kurz nach der letzten Dialysesitzung[62,67,107-109]. Die Ersten dieser Studien wurden jedoch durchgeführt, als noch Acetatdialysat[107-109] verwendet wurde, im Gegensatz zur heutigen Verwendung von Bicarbonatdialysat. Die kognitive Leistung von Hämodialysepatienten hängt von vielen Faktoren ab, u.a. von der Testumgebung. Sie fällt am besten aus, wenn die Tests in einem separaten Raum durchgeführt werden[110].

Da dies jedoch im Alltag nicht immer möglich ist, haben wir in einer weiteren Studie unter realen Dialysebedingungen (d.h. in einem Raum mit zwei oder drei anderen Patienten) untersucht, ob es einen signifikanten zeitabhängigen Effekt der kognitiven Leistungsfähigkeit gibt. Ziel unserer Studie war es, die Variabilität der kognitiven Leistung in Abhängigkeit vom Testzeitpunkt zu prüfen. Die Hauptfrage war, ob es einen optimalen Zeitpunkt für die Untersuchung der kognitiven Leistungsfähigkeit von Dialysepatienten gibt. Dieser Zeitpunkt sollte als Grundlage für künftige Forschungen auf dem Gebiet der kognitiven Beeinträchtigung bei Dialysepatienten dienen. Die neurokognitiven Tests wurden jeweils im Abstand von 14 Tagen in den ersten 2 Stunden der Dialyse (T1), in den letzten 2 Stunden der Dialyse (T2) und an dialysefreien Tagen durchgeführt (T3). Die Ergebnisse unserer Studie zeigten, dass der Zeitpunkt der Messung der kognitiven Funktion mit dem neurokognitiven Test „Repeatable Battery for the Assessment of Neuropsychological Status“ (RBANS) bei Hämodialysepatienten keine klinischen Auswirkungen auf die kognitive Leistungsfähigkeit hatte (A2) (Abbildung 1)[68].

Es wurden keine statistisch messbaren Unterschiede in der kognitiven Leistungsfähigkeit in den Gesamtergebnissen (Gesamtskala) festgestellt. Bei Betrachtung der einzelnen Domänen zeigte sich indes eine schlechtere kognitive Leistung in der Domäne Sprache (Language) am dialysefreien Tag (T3) im Vergleich zu den beiden übrigen Testzeitpunkten während der Dialyse (T1 und T2) (Abbildung 1)[68].

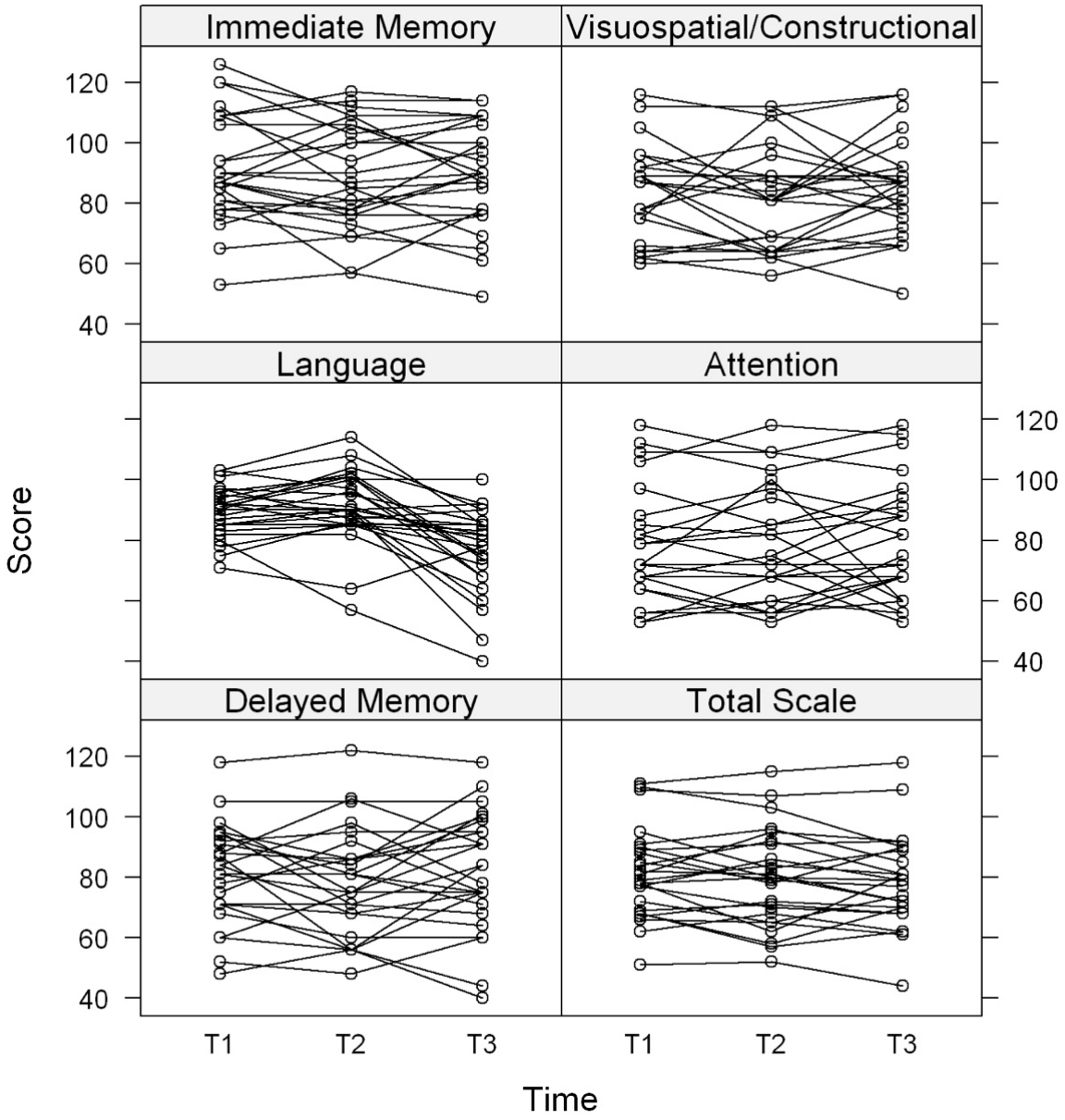


Abbildung 1: Index-Scores der einzelnen Domänen und des Gesamt-Scores. Dargestellt sind die einzelnen Zeitpunkte der Testungen (T1–T3). In der Gesamtskala (Total Scale) sowie in den Domänen Kurzzeitgedächtnis (Immediate Memory), Visuokonstruktion (visuospatial/constructional), verbales Langzeitgedächtnis (delayed memory) und Aufmerksamkeit (Attention) sind keine Unterschiede in den Index-Scores zu erkennen. In der Domäne Sprache/Wortflüssigkeit (Language) zeigt sich jedoch ein signifikanter Unterschied zwischen den Testzeitpunkten T1 vs. T2 ($p < 0{,}001$) und Testzeitpunkt T1 vs. T3 ($p < 0{,}001$).

T1 = Testzeitpunkt 1, erste 2 Stunden an der Dialyse, T2 = Testzeitpunkt 2, letzte 2 Stunden an der Dialyse, T3 = Testzeitpunkt 3, dialysefreier Tag

Im Gegensatz zu unseren Ergebnissen berichteten frühere Studien, dass der „optimale“ Zeitpunkt für die Durchführung des Tests 24 Stunden nach der Dialyse ist[67,111]. Die Dialysebehandlungen der Vergangenheit, die auf die Zeiten der Acetatdialyse[67] zurückgehen, sind jedoch nicht mit den heutigen modernen

Behandlungen der Dialyse mit Bicarbonat zu vergleichen. Übelkeit und Erbrechen waren bei den Patienten bei Anwendung dieser älteren Methoden sehr häufig, was eine mögliche Erklärung dafür sein könnte, dass sie an den dialysefreien Tagen bessere Testergebnisse erzielten.

Eine Studie von Murray et al.[111] aus dem Jahr 2007 mit 30 Dialysepatienten zeigte, dass die besten kognitiven Leistungen an einem dialysefreien Tag erzielt wurden und dass die ersten Stunden der Dialyse mit signifikant schlechteren kognitiven Leistungen assoziiert waren. Während die Sprache nicht beeinträchtigt war, wurde im Bereich der exekutiven Funktionen (Kontrollprozesse, die eingesetzt werden, wenn automatisiertes Handeln zur Problemlösung nicht mehr ausreicht. Hier ist anstatt routiniertem Vorgehen ein hohes Maß an bewusstem und aufmerksamen Handeln gefragt, wofür die exekutiven Funktionen notwendig sind) moderater Unterschied in der kognitiven Leistung festgestellt[111]. Ein möglicher Grund für die abweichenden Ergebnisse in unserer Studie könnte sein, dass alle Patienten zu den vorgegebenen Testzeitpunkten über einen Zeitraum von 6 Wochen getestet wurden, während in der Studie von Murray et al. die Zahl der Patienten, die nicht alle Tests absolvierten, größer war (15 von 33 Patienten wurden nicht in allen Testsitzungen getestet)[111].

Die Verwendung unterschiedlicher Studiendesigns könnte eine weitere Erklärung für die unterschiedlichen Ergebnisse sein. Um mögliche Lerneffekte bei den kognitiven Testungen zu vermeiden, ließen wir einen Zeitraum von 14 Tagen zwischen den einzelnen Testungen verstreichen, wählten eine Testbatterie für wiederholte Messungen aus (drei verschiedene validierte Versionen), die bei T1, T2 und T3 eingesetzt wurde, und legten die Reihenfolge der Testsitzungen T1, T2 und T3 für jeden Patienten fest.

In der Literatur gibt es einige Studien (mit leicht modifizierten Testzeitpunkten), die mit unseren Testergebnissen übereinstimmen[112,113]. Die Abnahme der kognitiven Leistungsfähigkeit am dialysefreien Tag konnte in einer anderen Studie[67] ebenfalls nachgewiesen werden. Der Grund dafür scheint derzeit wissenschaftlich noch nicht ausreichend erforscht zu sein. Hämodynamische Schwankungen, die als Ursache hierfür postuliert werden[68], halten wir für unwahrscheinlich, da die Verschlechterungen, die wir in der Domäne Sprache festgestellt haben, an den dialysefreien Tagen auftraten. Stattdessen könnte die Anhäufung von Giftstoffen an den dialysefreien Tagen für die kognitiven Veränderungen verantwortlich sein[68]. Zur endgültigen Beantwortung dieser Frage sind jedoch weitere Studien erforderlich.

In einer neueren Studie wurde auch die kognitive Leistung von Hämodialysepatienten während der Dialyse und am Tag nach der Dialyse untersucht [114]. Die Autoren stellten die Hypothese auf, dass eine einmalige Dialyse die kognitiven Funktionen von Hämodialysepatienten verbessert. Sie zeigten tatsächlich eine verbesserte Leistung im logischen und visuellen Langzeitgedächtnis nach der Dialysesitzung. Doch wie in unserer Studie veränderten sich weder die Leistung im Kurzzeit- und im Arbeitsgedächtnis noch die verbale Gewandtheit und das Planungsverhalten.

Ein fast ähnliches Studiendesign mit Tests vor der Dialyse und am Tag danach, verbunden mit einer Verbesserung der kognitiven Funktionen nach der Hämodialyse, insbesondere der Aufmerksamkeit, wurde von Griva et al.[62] beschrieben, wobei das Patientenkollektiv in den Studien deutlich jünger war und dies als Ursache für die unterschiedlichen Ergebnisse zu sehen ist[62,114]. Dasgupta et al.[91] berichteten indes, dass die kognitive Leistungsfähigkeit bei der Mehrzahl der Patienten während der Hämodialysebehandlung deutlich eingeschränkt ist. Obwohl die kognitive Leistungsfähigkeit mit unterschiedlichen Testversionen getestet wurde, wurden die Testungen selber innerhalb einer Dialysebehandlung durchgeführt. Somit könnten die unterschiedlichen Ergebnisse zwischen unserer Studie und der Studie von Dasgupta mit den unterschiedlichen Abständen der Durchführung der Tests zusammenhängen[68].

Eine neuere Studie von Findlay et al.[92] konnte im Gegensatz zu unseren Ergebnissen einen Zusammenhang zwischen dem zerebralen Blutfluss und der kognitiven Leistungsfähigkeit mit einer signifikanten Abnahme in den exekutiven Funktionen während der Dialysebehandlung nachweisen. Erklärbar ist dies möglicherweise durch die signifikant niedrigere Anzahl an Patienten mit Hypertonie in unserer Studie, die weniger empfindlich auf Blutdruckschwankungen reagierten[68].

Unabhängig vom Zeitpunkt der Untersuchung wiesen unsere Studienteilnehmer eine hohe Prävalenz kognitiver Beeinträchtigungen auf, was in Übereinstimmung mit früheren Befunden steht[26,66,111,115].

Trotz einer guten Planung der Studie muss einschränkend angemerkt werden, dass die Studienpopulation mit 65 Jahren etwas jünger war als der Durchschnitt der Dialysepatienten, was sich auf die kognitive Leistungsfähigkeit auswirken könnte. Zudem zeigte sich eine Überrepräsentation von männlichen Probanden in unserer Studie, wodurch die Ergebnisse möglicherweise nicht auf das allgemeine Patientenkollektiv übertragbar sind. Außerdem ist zu beachten, dass die

Untersuchungen in deutscher Sprache durchgeführt wurden und die Ergebnisse daher nicht auf alle demografischen Gruppen (z.B. Patienten mit Migrationshintergrund) verallgemeinert werden können[68]. Daher haben wir nur deutschsprachige Muttersprachler in unserer Studie eingeschlossen.

Die großen Vorteile der Studie liegen jedoch in dem prospektiven, bez. der Testreihenfolge randomisierten Studiendesign und in der Durchführung einer umfangreichen neurokognitiven Testbatterie, der Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), die bei der Erkennung leichter kognitiver Beeinträchtigungen sensitiver ist als Screening-Tests. Lerneffekte konnten durch Benutzen dreier unterschiedlicher Versionen ausgeschlossen werden konnten[116].

2.1.3. Mögliche Risikofaktoren und Behandlungsansätze von kognitiven Beeinträchtigungen bei Patienten vor und nach Nierentransplantation

Vor dem Hintergrund der hohen Prävalenz von kognitiven Beeinträchtigungen bei Dialysepatienten[64] und der Tatsache, dass die kognitive Leistungsfähigkeit sich mit zunehmender Einschränkung der Nierenfunktion verschlechtert (bereits bei einer eGFR von 60ml/min zeigt sich eine Einschränkung der kognitiven Leistungsfähigkeit)[20] stellte sich die Frage, ob sich die kognitive Leistungsfähigkeit nach einer Nierentransplantation und somit nach Verbesserung der Nierenfunktion auch ändert bzw. verbessert. Hierzu haben wir eine Studie konzipiert, in der wir die kognitive Leistungsfähigkeit bei nierentransplantierten Patienten, die zuvor eine Hämodialysetherapie erhalten hatten, mit einer differenzierten neurokognitiven Testbatterie untersuchten (A3)[76]. Die Untersuchung lässt sich gut in den klinischen Alltag integrieren und kann dazu beitragen, kognitive Beeinträchtigungen frühzeitig zu detektieren. Die bei nierentransplantierten Personen bislang verwendeten Tests [70,74,117,118] (Brief Cognitive State Examination, Montreal-Cognitive Assessment (MoCA) und 3MS, Modified Mini-Mental State Examination), die in der Literatur zu finden sind, sind nur Screening-Tests und unterschätzen möglicherweise das Ausmaß der kognitiven Beeinträchtigung. Da es derzeit keine standardisierte Testbatterie für nierentransplantierte Personen gibt, haben wir verschiedene validierte Tests ausgewählt, um die unterschiedlichen kognitiven Domänen zu bewerten. Auf diese Weise wird es möglich sein, die Entwicklung kognitiver Beeinträchtigungen bei

nierentransplantierten Personen zu beurteilen und ein klares Profil der kognitiven Funktion der untersuchten Population zu erstellen.

Die Studie, welche sich aktuell in der Rekrutierungsphase befindet, gliedert sich in mehrere Teile. Teil A untersucht die auf der Warteliste stehenden Patienten vor und nach der Transplantation. In Teil B werden bereits transplantierte Patienten getestet[76]. In beiden Studienarmen werden Patienten nach postmortaler- und Lebendnierentransplantation eingeschlossen. Anämie, sekundärer Hyperparathyreoidismus und urämische Toxine (UT) wurden als Hauptursachen für kognitive Beeinträchtigungen im Zusammenhang mit chronischen Nierenerkrankungen genannt[119], ebenso wie die Dialysedauer[100]. Wir gehen davon aus, dass sich diese Parameter nach einer Transplantation verbessern, und wollen die Auswirkungen dieser Parameter auf die kognitive Funktion untersuchen[76].

Aufgrund der Ergebnisse eigener Vorarbeiten bei Dialysepatienten[64] sowie anderer Studien[100,104,105] wissen wir, dass Patienten mit Depressionen eine signifikant niedrigere kognitive Leistungsfähigkeit aufweisen. Dies lässt sich durch die Auswirkungen der Depressionssymptome auf kognitive Bereiche wie exekutive Funktionen und Verarbeitungsgeschwindigkeit erklären[105,120]. Um die Häufigkeit von Depressionen und deren Auswirkung auf die kognitive Leistungsfähigkeit zu ermitteln, wird in der aktuellen Studie der Fragebogen der sogenannten Hospital Anxiety and Depression Scale – Deutsche Version (HADS-D-26-Test) herangezogen. Dabei stellen wir die Hypothese auf, dass transplantierte Personen mit Depressionen signifikant höhere kognitive Beeinträchtigungen aufweisen als transplantierte Personen ohne Depressionen[76].

Des Weiteren konnte eine kürzlich durchgeführte Meta-Analyse zeigen, dass subjektiver Stress die Entwicklung kognitiver Beeinträchtigungen beeinflusst[121]. Ein wahrscheinlicher Vermittler des Zusammenhangs zwischen Stress und kognitiver Leistung, aber auch zwischen Depression und kognitiver Leistung, ist die Aktivität der HHNA-Achse. Dies ist ein stress-responsives System, und die Aktivität dieser Achse wird in der Regel über ihr Endprodukt Cortisol gemessen wird. Es wurde festgestellt, dass überschüssiges Cortisol schädliche Auswirkungen auf das limbische System hat, was zu einer Beeinträchtigung der Lernmechanismen führt[122]. Einige Studien deuten auch darauf hin, dass höhere Cortisolwerte bei Menschen mit Depressionen mit einer geringeren Verarbeitungsgeschwindigkeit einhergehen[123,124]. Im Einklang damit wurde in einer Studie ein negativer Zusammenhang zwischen Haar-Cortisol und kognitiver

Leistung nach einem Schlaganfall festgestellt[125]. Haar-Cortisol als Marker für die Aktivität der HHNA-Achse (und damit als Marker für Stress) ist von besonderem Interesse, da es die kumulative Aktivität der HHNA-Achse in den Monaten vor dem Messzeitpunkt (in unserem Fall vor der Nierentransplantation) widerspiegelt[126]. Uns ist keine Studie bekannt, in der der Zusammenhang zwischen subjektivem Stress und Haar-Cortisol (objektivierbarer Stressmarker) oder deren Wechselwirkung mit Depressivität bei nierentransplantierten Personen untersucht wurde.

Ziel unserer Studie ist es, a) das Ausmaß der kognitiven Beeinträchtigung, b) den Verlauf der kognitiven Leistung bei nierentransplantierten Personen und c) das Profil der kognitiven Beeinträchtigung zu untersuchen (d. h. ob ein bestimmter kognitiver Bereich stärker betroffen ist als andere). Darüber hinaus untersuchen wir die Auswirkungen und den zeitlichen Verlauf von Variablen, die einen potenziellen Einfluss auf die kognitive Leistungsfähigkeit haben, als sekundäre Forschungsfragen. In diesem Zusammenhang sind Variablen im Zusammenhang mit Stress (subjektiver Stress, Depression und langfristige Aktivität des Hypothalamus-Hypophysen-Nebennieren-Achse (HHNA)) von besonderem Interesse für uns.

Untersucht werden sowohl Patienten, die eine Niere von einem verstorbenen Spender erhalten, als auch Personen nach Lebendnierenspende. Um eine Auswirkung der Transplantation zu erkennen, werden die Tests zeitnah zur Transplantation durchgeführt. Die neurokognitiven Tests werden bei Lebendnierenspendern innerhalb von 14 Tagen vor der geplanten Transplantation durchgeführt. Bei Personen, die eine postmortale Spende erhalten, ist eine vorherige Terminierung der neurokognitiven Tests nicht möglich. Nachdem die Personen auf die Warteliste gesetzt wurden, beträgt die Wartezeit für eine Nierentransplantation durch einen verstorbenen Spender in Deutschland in der Regel 6–8 Jahre[127], sodass ein Test bei der Aufnahme in die Warteliste nicht praktikabel ist. Daher haben wir beschlossen, die Tests bei der Aufnahme von Personen zur Nierentransplantation während der Dialyse vor der Transplantation durchzuführen – auch, da unsere Vorarbeiten zeigen konnten, dass die Testergebnisse durch die Dialyse nicht beeinflusst werden[68].

Trotz der sorgfältigen Planung gibt es bei der vorliegenden Untersuchung einige Einschränkungen. Die Testumgebung ist für Personen, die eine Niere von einem verstorbenen Spender erhalten, möglicherweise nicht optimal (der Patient könnte unter einer außerordentlichen psychischen Belastung und Nervosität stehen). Es wäre ideal gewesen, diese Personen 1 oder 2 Wochen vor der Transplantation zu testen, aber

das ist nicht möglich, da nicht bekannt ist, wann diese Personen ihre Transplantationsangebote erhalten werden. Es scheint außerdem möglich, dass die Antworten auf der HADS-Skala (Hospital Anxiety and Depression Scale) durch die positive Nachricht über die Transplantation beeinflusst werden könnten. Wir vermuten, dass dieser Einfluss bei Personen, bei denen eine Transplantation nicht geplant ist (Nierentransplantation durch einen verstorbenen Spender), stärker ausgeprägt ist als bei Personen, bei denen eine Transplantation geplant ist (Lebendspende).

Die Ergebnisse unserer Studie könnten potenziell wichtige Auswirkungen auf die Prävention und Behandlung kognitiver Beeinträchtigungen bei nierentransplantierten Personen haben. Durch den Zuwachs an Wissen über das neurokognitive Profil und die Zuordnung der entsprechenden Defizite könnte es möglich werden, ein individualisiertes Trainingsprogramm zu erstellen, um die kognitiven Defizite dieser Personen positiv zu beeinflussen[76].

2.2. Immunologische Aspekte der chronischen Niereninsuffizienz

2.2.1. Retransplantation einer zuvor transplantierten Niere - eine sichere Strategie in Zeiten des Organmangels?

Die Nierentransplantation ist nach wie vor die beste Therapie für Patienten mit terminaler Niereninsuffizienz. Sie wird jedoch durch den in Deutschland erheblichen Mangel an Nierenspenden eingeschränkt, der in den letzten Jahren weiter angestiegen ist[37]. Die Versuche, die Zahl der verstorbenen und lebenden Spender zu erhöhen (Eurotransplant-Senior-Programms[9,48], die Doppelnierentransplantation[49] oder auch die Verwendung von Nieren mit schwerem akutem Nierenversagen[50,51]), blieben in ihrem Erfolg bisher begrenzt.

Aus US-Registerdaten ist bekannt, dass zwischen 20–25 % der Patienten, die ein Nierentransplantat erhalten, mit einem funktionierenden Nierentransplantat versterben[78,79,128]. Diese Daten belegen, dass der Pool an verstorbenen Spendernieren groß ist und eventuell deutlich zu wenig genutzt wird. Uns stellte sich die Frage, ob die Wiederverwendung einer bereits transplantierten Niere ein weiterer Ansatz sein könnte, um den Pool an Nierenspendern zu vergrößern und ob die Wiederverwendung einer bereits transplantierten Niere ein weiterer Ansatz sein

könnte, um den Pool an Nierenspendern zu vergrößern, der alle Anforderungen der Sicherheit erfüllt.

Hierfür führten wir eine Analyse in der Eurotransplant-Datenbank zwischen dem 1. Januar 1995 und dem 31. Dezember 2015 durch. Um diejenigen Nierenspender zu ermitteln, die zuvor eine Nierentransplantation erhalten hatten, wurden die Parameter ABO-Blutgruppe, Geschlecht, HLA-Antigene und Geburtsdatum von Nierenempfängern und Nierenspendern verglichen. Die Anzahl der angebotenen und schließlich akzeptierten Nierentransplantate zur Retransplantation wurde analysiert, ebenso wie die Gründe für die Ablehnung solcher Nierentransplantate erfasst[86], und die Empfänger des zweiten Transplantats wurden bis zum Verlust des Transplantats oder bis zum Ableben des Patienten nachverfolgt. Die Daten zu Abstoßungsreaktionen und den Nierentransplantat-Biopsiebefunden (soweit verfügbar) wurden gesammelt. Nur 9 von insgesamt 68.554 allozierten Nieren waren zuvor transplantiert worden. 4 dieser 9 Nieren wurden schließlich noch einmal transplantiert. Das mittlere Intervall zwischen der ersten Transplantation und dem Angebot einer erneuten Transplantation betrug 1689 ± 1682 Tage (SD, standard deviation); Range 55–5.333 Tage). Zum Zeitpunkt der ersten Transplantation betrug das mittlere Serumkreatinin der Spender 1,0 mg/dl (0,6–1,3 mg/dl) und bei der zweiten Transplantation 1,4 mg/dl (0,8–1,5 mg/dl). Das mittlere Transplantatüberleben betrug beim ersten Empfänger 50 Monate (2–110 Monate) und beim zweiten Empfänger 111 Monate (40–215 Monate)[86].

Unsere Daten ließen erkennen, dass Patienten, die bereits transplantiert wurden, nur selten wieder als Spender in Betracht gezogen werden. Möglicherweise ist das Bewusstsein noch nicht dafür geschärft worden, solche Organe als transplantierbar zu betrachten. Dies betrifft entweder das Spenderzentrum, sodass die Organe gar nicht erst für eine erneute Transplantation in Betracht gezogen werden, oder das potenzielle Empfängerzentrum, das unter Umständen Bedenken wegen chronischer histologischer Prozesse hat, die den Erfolg der Retransplantation beeinträchtigen könnten. Es gibt natürlich auch viele andere Gründe, warum ein Patient mit einem Transplantat nicht als Spender in Frage kommt, obwohl er mit einer funktionierenden Spenderniere verstirbt. Patienten, die außerhalb des Krankenhauses sterben, und multimorbide Patienten kommen in der Regel nicht für eine Organspende in Betracht. Die fünf häufigsten Todesursachen bei Patienten mit einem funktionierenden Transplantat sind kardiovaskuläre Ereignisse, Infektionen, Tumore, zerebrovaskuläre Erkrankungen und Blutungen[128]. West et al.[129] fanden heraus, dass 22 % dieser

Patienten an einer Infektion, 17 % an einem Myokardinfarkt und 15 % an einem plötzlichen Tod starben. Patienten, die an einer aktiven bösartigen Tumorerkrankung oder einer aktiven Infektion wie Meningitis oder HIV gestorben sind, kommen für eine Nierenspende nicht in Frage.

Trotz dieser zahlreichen Einschränkungen gehen wir davon aus, dass die Zahl der in Betracht kommenden Spender in der Eutrotransplant-Region zwischen 1995 und 2015 höher war als die von uns gemeldeten 9 Patienten. Obwohl genauere Daten zu diesem Thema fehlen, werden potenzielle Kandidaten für die Retransplantation einer zuvor transplantierten Niere in unseren Intensivstationen möglicherweise nicht berücksichtigt. Daher sollten die Daten zu diesem Problem nicht nur von den nationalen Organspendeorganisationen gesammelt werden, es sollten auch verstärkt Anstrengungen unternommen werden, um auf den Intensivstationen über dieses Thema aufzuklären.

Die Daten unserer 4 realisierten Fälle haben gezeigt, dass selbst Nieren, die bereits vor langer Zeit transplantiert wurden, nach dem Hirntod des ersten Empfängers erneut erfolgreich in einen anderen Empfänger transplantiert werden können[86]. Von dieser Möglichkeit wurde in der Vergangenheit jedoch nur selten Gebrauch gemacht. Nur wenige Einzelfälle der Transplantation einer zuvor transplantierten Niere sind veröffentlicht worden[79,81-85,130-132], systematische Analysen sind bislang überhaupt noch nicht veröffentlicht worden. Des Weiteren ist über das Langzeit-Outcome der berichteten Retransplantation nicht viel bekannt. Meist gibt es nur Kurzzeitergebnisse bis zu einem Jahr nach der Transplantation[79,83,84,130,132] und in nur wenigen Fällen wurde eine Nachbeobachtungszeit von 1–4 Jahren bzw. in 2 Fallberichten eine Nachbeobachtungszeit von 5[85] bzw. 12 Jahren[131] beschrieben. Alle veröffentlichten Fälle wiesen in der Nachbeobachtungszeit eine gute Transplantatfunktion auf.

Ob die Dauer des Transplantatüberlebens nach der ersten Transplantation einer Niere einen Einfluss auf das Transplantatüberleben nach einer Retransplantation hat, ist nicht klar. In unseren Fallberichten wird zum ersten Mal eine Nachbeobachtungszeit angegeben, bis der zweite Empfänger erneut dialysepflichtig wird oder stirbt[86].

Unsere Studie ließ tatsächlich vermuten, dass das Überleben des Nierentransplantats möglicherweise davon beeinflusst wird, wie lange das erste Transplantat beim ersten Empfänger überlebt hat[86]. Aufgrund der geringen Fallzahl kann eine definitive Aussage jedoch nicht getroffen werden, da insbesondere zuverlässige histologische Daten

fehlen, die eine Zunahme chronischer Schäden im Zusammenhang mit dem Transplantatüberleben nach der ersten Transplantation zeigen könnten.

In den wenigen Fällen, über die in der Literatur berichtet wird, scheint die Dauer der Transplantatfunktion beim ersten Empfänger keinen eindeutigen Einfluss auf das Transplantatüberleben beim zweiten Empfänger zu haben. Allerdings war die Nachbeobachtungszeit in vielen Fallberichten, wie bereits erwähnt, nur kurz. Die berichteten Fälle zeigten eine lange und gute Transplantatfunktion (Serumkreatinin 1,3 mg/dl) auch beim zweiten Empfänger (9 Jahre[84], 8 Jahre[85] und 6 Jahre[131]).

Unsere Daten belegten, dass die Transplantation einer Niere, die bereits zuvor transplantiert wurde, erfolgreich sein kann. Unseres Wissens wurde bisher auch kein Bericht veröffentlicht, laut dem die Retransplantation einer zuvor transplantierten Niere nicht erfolgreich war. Unsere Daten aus der Datenanalyse der Eurotransplant-Region mit 4 erfolgreichen Transplantationen und Transplantatüberlebenszeiten zwischen 3 und 18 Jahren haben diese Annahme[86] bestätigt, obwohl ein Publikationsbias in Regionen außerhalb von Eurotransplant möglich sein könnte. Im Vergleich zu den akzeptierten Organen fiel auf, dass die eGFR der abgelehnten Organe in der Eurotransplant-Region zum Zeitpunkt des zweiten Angebots niedriger ist (statistisch nicht signifikant)[86]. Es zeigte sich aber auch, dass die Nierenfunktionen bereits zum Zeitpunkt der ersten Transplantation insgesamt niedriger waren[86]. Eine niedrige eGFR darf also nicht als einziger Grund für die Ablehnung eines Organs für eine erneute Transplantation herangezogen werden.

Mögliche Risikofaktoren für ein ungünstiges Transplantatüberleben sind wichtig zu kennen, wenn man Organangebote annimmt oder ablehnt. Eine Reihe chirurgischer Probleme sollten beachtet werden bei der Retransplantation einer bereits zuvor transplantierten Niere. So kann grundsätzlich ein ausgedehntes Narbengewebe den chirurgischen Zugang zur Spenderniere erschweren[86].

Im Rahmen einer regulären abdominalen Explantation wird regelhaft die Aorta abdominalis direkt unterhalb der Nierenarterien kanüliert und abgeklemmt. Aufgrund der geänderten Anatomie nach Nierentransplantation mit Ursprung der Nierengefäße aus den Iliakalgefäßen muss bei der Entnahme sichergestellt werden, dass die Nierengefäße der transplantierten Niere über die Arteria iliaca externa gespült werden. Das bedeutet, dass eine zusätzliche Kanüle nicht nur in der Aorta, sondern auch in die Arteria iliaca exterrna gelegt werden muss. Es sollte ein Patch der Spender-Iliakalarterie und -vene entnommen werden, um die ursprüngliche Gefäßlänge zu

erhalten. Wenn um die ursprüngliche Anastomose herum Verwachsungen vorhanden sind, sollten die Gefäße im Anastomosenbereich nicht durchtrennt werden[86]. Außerdem könnte durch Beschneiden des iliakalen Patches an Arterie und Vene eine Anastomose mit größerem Volumen geschaffen werden. Da die Nierengefäße bereits einmal durchtrennt worden sind, könnte eine erneute Transplantation zu einer weiteren Verkürzung dieser Gefäße führen[86]. Je nach Verwachsungen muss der Harnleiter verkürzt werden und gegebenenfalls direkt auf den Empfängerureter anastomosiert werden. Dies kann aus anatomischen Gründen hinsichtlich der Blutversorgung des Harnleiters zu einer höheren Komplikationsrate in Form von Insuffizienzen oder Stenosen führen[86].

Es ist außerdem zu bedenken, dass das Fortschreiten einer Seneszenz (Alterungsprozess) nach der Retransplantation einer zuvor transplantierten Niere durch wiederholte Ischämie-Reperfusionsschäden beschleunigt werden kann, insbesondere bei Transplantaten, die nach der ersten Transplantation chronische Schäden erlitten haben[133,134]. Die retransplantierten Nieren in unseren Fällen waren zum Zeitpunkt der Retransplantation relativ jung und konnten daher den oxidativen Stress und die akute Nierenschädigung nach der Transplantation besser bewältigen als ältere Nieren[135]. Es scheint jedoch schwierig zu sein, das Ausmaß der bestehenden chronischen Schäden einer bereits transplantierten Niere zum Zeitpunkt eines solchen Organangebots vorherzusagen, ohne eine Biopsie durchzuführen. Andererseits gibt es trotz des weit verbreiteten Einsatzes von Biopsien vor der Implantation keinen Konsens über ihren Wert bei der Vorhersage des Überlebens von Allotransplantaten[136,137].

Aus den gesammelten Daten zum Transplantatergebnis in unserer Serie und auch aufgrund der veröffentlichten Fallberichte schlagen wir vor, dass das Angebot einer bereits transplantierten Niere sorgfältig erwogen werden sollte, insbesondere bei eher jungen Erstspendern mit derzeit guter Transplantatfunktion des Erstempfängers[86]. Dabei sollte selbst bei normalem Serumkreatinin und bei fehlender Proteinurie und Albuminurie vor der Transplantation eine sogenannte Nullbiopsie durchgeführt werden, um größere chronische Schäden auszuschließen. Die Tatsache, dass eine Niere bereits vor langer Zeit transplantiert worden ist, sollte nicht unbedingt ein Grund sein, ein solches Transplantat abzulehnen. Da bereits transplantierte Nieren im neuen Empfänger lange überleben können, sollten solche Organe zudem nicht generell nur

für ältere Empfänger in Betracht gezogen werden, sondern in sorgfältig ausgewählten Fällen auch für jüngere[86].

2.2.2. Zelluläre und humorale Immunantwort im Rahmen von mRNA- und Vektor-basierten Covid-19 Impfungen bei Dialysepatienten

Patienten mit terminaler Niereninsuffizienz haben per se ein herabgesetztes Immunsystem[138,139]. Dasselbe gilt für Patienten nach Nierentransplantationen durch die Einnahme von immunsuppressiven Medikamenten[56]. Es ist bekannt, die Immunantwort dieser Patienten nach Impfungen (z.B. Hepatitis B) herabgesetzt ist[140]. Nachdem die Impfstoffe gegen das neue Coronavirus-19 von der europäischen Arzneimittelagentur (EMA, European Medicines Agency) zugelassen wurden[57] und eine gute humorale Immunantwort in der Normalbevölkerung zeigen[58,59], kam die Frage auf, ob sich bei Dialysepatienten auch eine robuste Immunantwort entwickelt. Außerdem sollte herausgefunden werden, ob im Rahmen einer humoralen Impfantwort auch auf die Ausbildung einer zellulären Impfantwort geschlossen werden kann. Deswegen haben wir prospektive Studien bei Dialysepatienten durchgeführt, in denen wir die humorale und zelluläre Immunantwort sowohl 4 Wochen (T1) und 6 Wochen (T2)[87,88] nach der vollständigen Grundimmunisierung als auch 6 Monate nach der Grundimmunisierung (und vor einer Booster-Impfung) (T3) und 4 Wochen nach einer Booster-Impfung[89] quantifiziert haben. Dies wird im Folgenden beschrieben.

2.2.2.1. Beurteilung der zellulären und humoralen Immunogenität und Reaktogenität mRNA-basierter und vektor-basierter Covid-19-Impfstoffe bei Dialysepatienten mittels Elispot-Assay, sowie Antikörper-Chemilumineszenz-Mikropartikel-Immunoassay und Dot-Plot-Arrays

Die SARS-CoV-2-spezifische zelluläre Immunantwort wurde mit IFN-γ- und IL-2-ELISpot-Assays bewertet. Die SARS-CoV-2-spezifische humorale Immunantwort wurde mit einem Dot-Plot-Array und einem chemilumineszenten Mikropartikel-Immunoassay bewertet[88].

Hierfür wurden Blutproben für die Isolierung peripherer mononukleärer Blutzellen (PBMC) in Natriumzitratröhrchen gesammelt und innerhalb von 24–48 Stunden nach der Blutentnahme verarbeitet. Vollblut wurde im Verhältnis 3:1 mit

Phosphatpuffersalzlösung (PBS; Biochrom GmbH, Berlin, DE) verdünnt, um Gerinnung zu vermeiden, und auf Ficoll-Paque Plus (GE Healthcare Bio-Sciences AB, Uppsala, SE) geschichtet. Die Proben wurden bei 1000 × g für 30 Minuten bei Raumtemperatur mit abgeschalteter Bremse zentrifugiert. Die PBMC-Schicht wurde gesammelt und dreimal gewaschen (zweimal PBS, einmal AIM-V (Thermo Fisher Scientific Inc., Waltham, US)). Schließlich wurden die Zellen gezählt und für die Verwendung im ELISpot-Assay auf 2 x 106 Zellen/ml eingestellt[88].

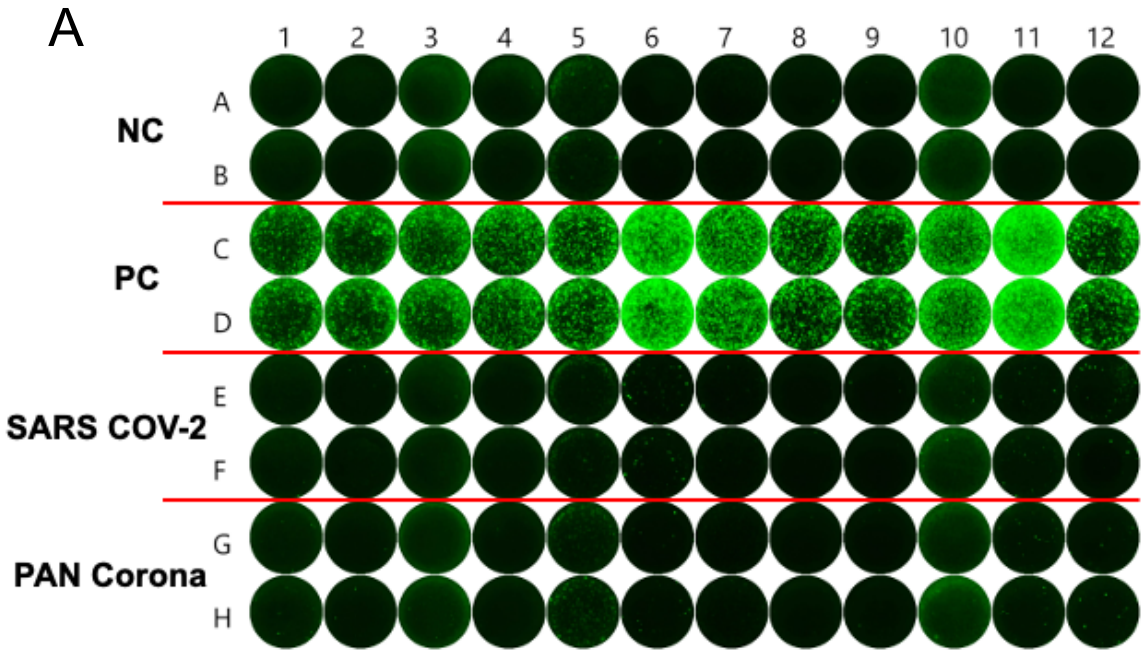
Alle ELISpot-Experimente wurden mit dem AID/GenID-CoV-iSpot-IFN-γ+IL-2-(ELSP7010)-Nachweiskit durchgeführt. Kurz gesagt, es wurden 96-Well-Membranplatten mit Capture-Antikörpern gegen humanes IFN-γ und humanes IL-2 beschichtet. Für die Negativkontrolle wurden die Zellen in Zellkulturmedien ohne Zugabe von Stimulanzien inkubiert. Pokeweed-Mitogen wurde als Positivkontrolle verwendet. Zur Co-Stimulation wurde Anti-CD28 in jede Vertiefung gegeben[88].

Aufgrund der hohen Homologien zwischen SARS-CoV-2, SARS-CoV, dem Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) und anderen Coronaviren, die Erkältungskrankheiten verursachen, ist besondere Vorsicht geboten, um ausschließlich eine SARS-CoV-2-spezifische Immunität nachzuweisen. Das AID/GenID-CoV-iSpot-Kit enthält einen SARS-CoV-2-spezifischen Peptid-Pool mit maximalen Unterschieden zu anderen Coronaviren als SARS-CoV-2 (SARS-CoV-2-Peptid-Mix) und einen zusätzlichen Peptidpool mit einem maximalen Konsens über verschiedene Typen der Coronaviridae-Familie (PAN-Corona-Peptid-Mix). Die Mehrzahl der SARS-CoV-2-spezifischen Peptide, die im AID/GenID-SARS-CoV-2-Peptid-Mix enthalten sind, befinden sich in der N-terminalen Region des Spike-Proteins, während die konservierten Regionen im PAN-Corona-Peptide-Mix die C-terminale Region darstellen. Darüber hinaus sind die verwendeten Antigen-Peptid-Pools nicht von den aktuellen Schlüsselmutationen 69-70 del, E484K, N501Y und D614G betroffen[88].

Für alle Proben wurden jede Kontrolle und Antigenstimulation in Duplikaten mit 2 x 105 PBMC/Vertiefung (oder 2x106 PBMC/ml) durchgeführt. Zur Stimulierung wurden die Platten 16–20 Stunden lang bei 37 °C und 5 % CO2 inkubiert. Am nächsten Tag wurden die Platten gemäß dem Herstellerprotokoll bearbeitet. Nach 5 Waschschritten wurden die Nachweisantikörper zugegeben und 2 Stunden lang bei Raumtemperatur in einer dunklen, feuchten Kammer inkubiert. Anschließend wurden 5 weitere Waschschritte durchgeführt, gefolgt von der Zugabe von fluoreszenzmarkierten

Antikörperkonjugaten, die 1 Stunde lang inkubiert wurden. Zuletzt wurde nach dem Waschen für 15 Minuten ein Fluoreszenzverstärker zugegeben. Am nächsten Tag wurde die vollständig getrocknete Platte mit einem AID/GenID-iSpot-spectrum-ELISpot-Reader zur Dokumentation und Auswertung der Ergebnisse abgelesen (Abbildung 2 A und B)[88].

Die Ergebnisse wurden durch Berechnung des Verhältnisses zwischen der antigenspezifischen Reaktion und der Negativkontrolle (NC) bewertet und so wurde der sogenannte Stimulationsindex (SI) berechnet. Jeder antigenspezifische FluoroSpot-Test mit einem SI von ≤2 (bei einer NC > 2) oder ≤5 (bei einer NC < 2), abhängig von der Hintergrundstimulation, wurde bei der quantitativen Bewertung als negativ angesehen. Bei einem NC > 2 wurde ein Stimulationsindex von > 5 - < 7 als grenzwertig und ein SI ≥ 7 als positiv angesehen, während bei einem NC ≥ 2 ein Stimulationsindex von > 2 - ≤ 3 als grenzwertig und ein SI > 3 als positiv angesehen wurde.



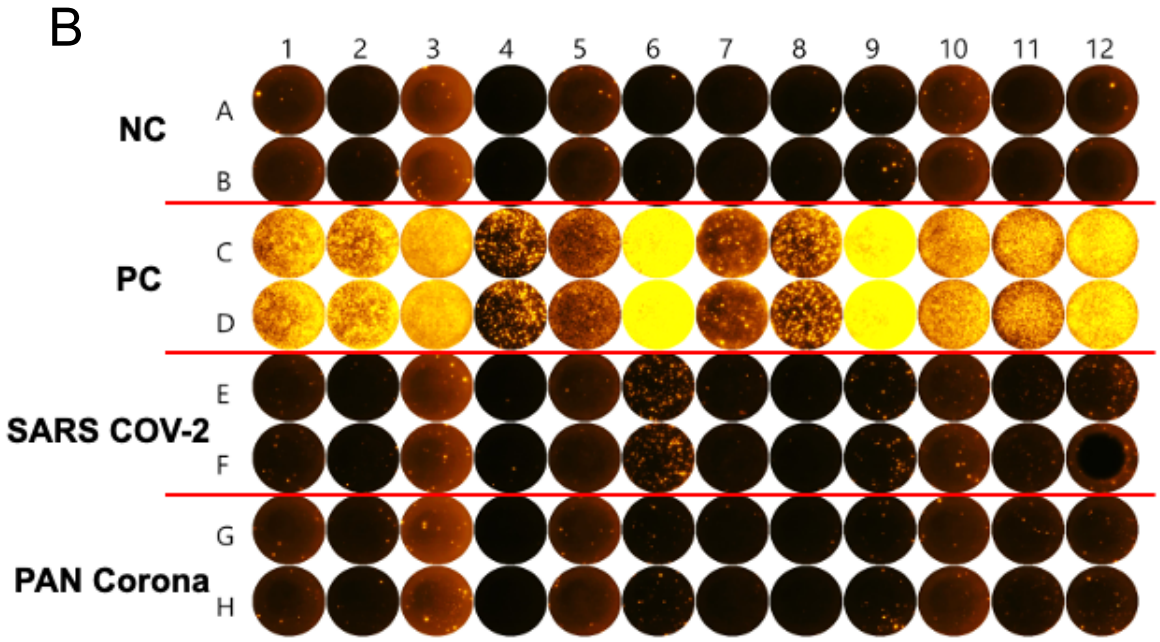


Abbildung 2: Darstellung der Platten des AID/GenID-iSpot-ELISpot. Abbildung A zeigt die Interferon-Gamma- und Abbildung B die Interleukin-2-spezifische T-Zell-Immunantwort. Dargestellt sind jeweils auf den Linien A und B die Negativkontrollen (NC), auf den Linien C und D die Positivkontrollen (PC), auf den Linien E und F die SARS-COV-2-spezifische Immunantwort und auf den Linien G und H die Immunantwort auf das PAN-Corona-Mix-Peptid.

Die Analyse der SARS-CoV-2-spezifischen Antikörper erfolgte unter Verwendung von Plasma aus zitrierten Vollblutproben mit einem Immunglobulin G (IgG)-Test, der mit einer rekombinanten rezeptorbindenden Domäne des SARS-CoV-2-Spike-Protein-Antigens beschichtet war, unter Verwendung eines hauseigenen Dot-Plot-Arrays der Firma GenID, das gegenüber den klinischen Daten verblindet war. Die Antikörperspiegel werden als prozentuale Intensität der Grauskala ausgedrückt, die von 0 bis 100 Prozent reicht, wobei eine Intensität von >16 % als positiv und ≤16 % als negativ angesehen wird (Abbildung 3).

Abbildung 3: Beispiele eines negativen (ID 17), schwach positiven (ID 23) und eines stark positiven (ID 36) Arrays.

Darüber hinaus wurden SARS-CoV-2-spezifische Antikörper aus Serumproben gegen das Spike-Protein und das Nukleokapsidprotein vom Institut für Medizinische Virologie (Universitätsklinikum Gießen, Deutschland) mittels Antikörper-Chemilumineszenz-Mikropartikel-Immunoassay (CMIA; Anti-S AdviseDx SARS-CoV-2 IgG II und Anti-N Abbott Architect SARS-CoV-2 IgG, Abbott, Chicago, IL, USA) bestimmt. Das Anti-N-Array (gemessen in S/CO) wurde zum Nachweis einer früheren Infektion verwendet. Die Anti-S-Spiegel nach einer Infektion oder Impfung wurden als AU (Arbitrary Unit)/ml ausgedrückt, wobei Werte >50AU/ml als positiv und ≤50 AU/ml als negativ definiert wurden.

2.2.2.2. Beurteilung der Immunogenität und Reaktogenität homologer mRNA-basierter und vektorbasierter SARS-CoV-2-Impfstoffregime bei Dialysepatienten nach Grundimmunisierung

An dieser prospektiven, monozentrischen Kohortenstudie nahmen Patienten im Alter von ≥ 18 Jahren teil, die dreimal wöchentlich eine Zentrumsdialyse (Hämodialyse) oder eine Peritonealdialysebehandlung im ambulanten Dialysezentrum der Patienten-Heimversorgung am Universitätsklinikum Gießen und Marburg, Standort Gießen, Deutschland, erhielten. Zum Zeitpunkt der Aufnahme in die Studie betreute das Dialysezentrum 84 Hämodialysepatienten und 5 Peritonealdialysepatienten[88]. Die Patienten wurden in die Studie aufgenommen, wenn sie: i) einen homologen mRNA-basierten oder einen vektorbasierten Einzel- oder Doppeldosis-Impfstoff (mit oder ohne Vorgeschichte von COVID-19) erhalten hatten und ii) mittels PCR eine aktuelle SARS-CoV-2-Infektion ausgeschlossen war. Der Abstand zwischen der ersten und der zweiten Injektion wurde gemäß den EMA-Leitlinien[57] festgelegt: 3–4 Wochen für homologe mRNA-basierte (BNT162b2 und mRNA-1273) Impfstoffe und 4–12 Wochen für die vektorbasierte Einzeldosis (Ad26.COV2.S) oder den homologen vektorbasierten ChAdOx1 nCoV-19-Impfstoff. Alle Blutproben wurden vor der Dialysebehandlung, und zwar 4 Wochen (T1) und 6 Wochen (T2) nach der vollständigen Impfung entnommen, mit einem Toleranzbereich von ± 2 Tagen. Lokale und systemische unerwünschte Ereignisse nach der ersten und zweiten Dosis wurden anhand eines standardisierten Fragebogens selbst erfasst[87].

Bei den meisten Patienten (91,7 %) waren zu mindestens einem Zeitpunkt SARS-CoV-2-Antispike-IgG-Antikörper nachweisbar. Die mit dem Abbott-Assay gemessenen medianen SARS-CoV-2-Antispike-IgG-Antikörperspiegel waren jedoch 6 Wochen

nach der Impfung deutlich niedriger als 2 Wochen zuvor, was darauf hindeutet, dass eine Vollimpfung zwar ausreichend war, um SARS-CoV-2-spezifische Antikörper zu induzieren, die Antikörperspiegel jedoch tendenziell schnell abnahmen (Abbildung 5)[87]. Obwohl nur 51,7 % der Patienten in den SARS-CoV-2-spezifischen ELISpot-Tests zur T-Zell-Aktivierung reaktiv waren, gab es keine nachweisbaren Unterschiede in den IL-2- oder IFN-γ-Reaktivitäten zwischen den beiden Zeitpunkten, was auf die kurzfristige Stabilität der zellulären Immunität im Vergleich zur humoralen Immunität nach der Vollimpfung hinweist (Abbildung 4)[87].

Schließlich zeigten Patienten, die 6 Monate nach einer SARS-CoV-2-Infektion eine Auffrischungsimpfung erhielten, im Vergleich zu SARS-CoV-2-naiven Patienten nach vollständiger Impfung sowohl eine bessere humorale als auch zelluläre Immunität, während Patienten mit immunsuppressiver Therapie (N=5) fast keine nachweisbare humorale oder zelluläre Immunität entwickelten (Abbildung 5 und Tabelle 1)[87].

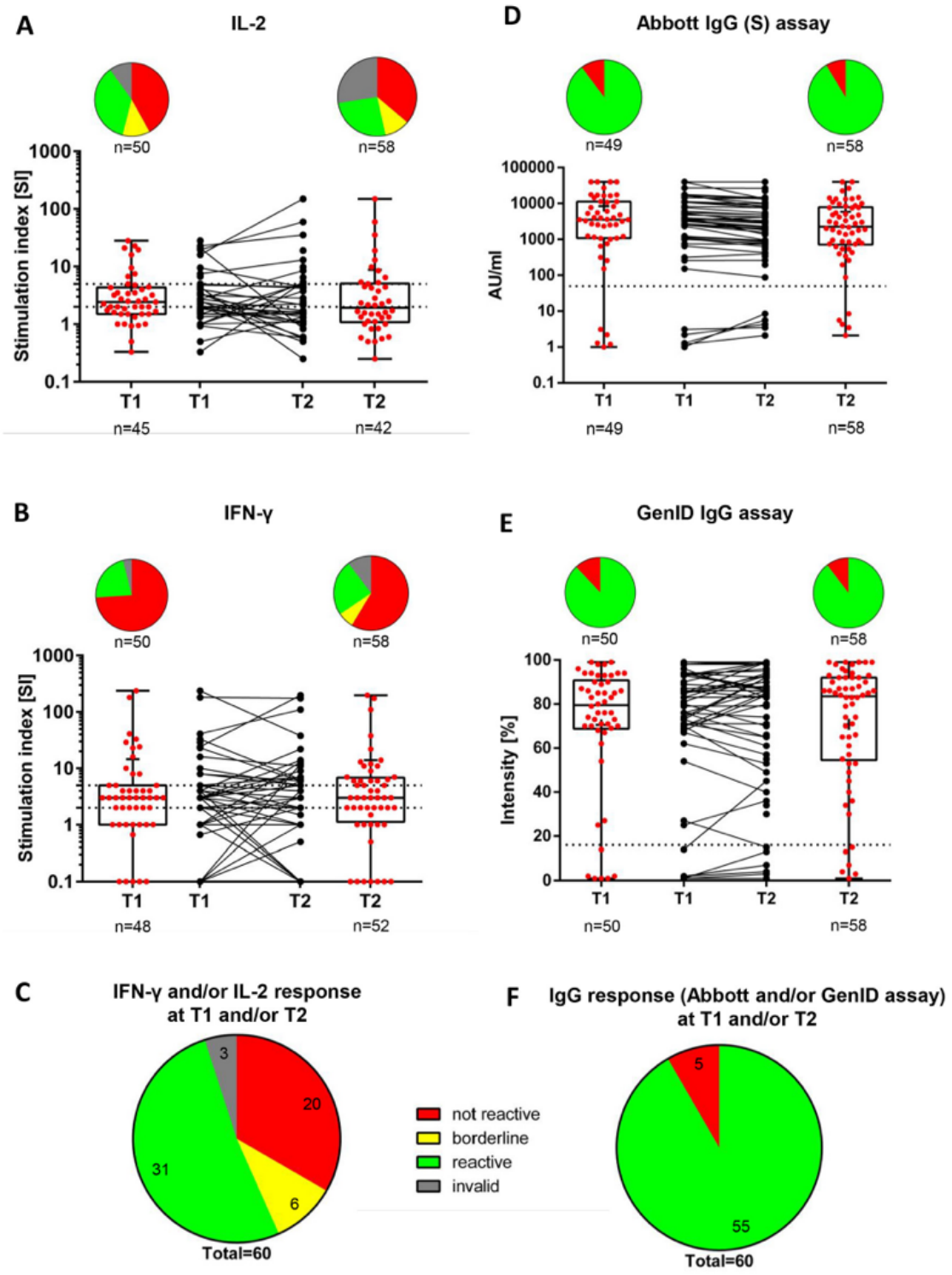


Abbildung 4: Dargestellt ist die impfstoffinduzierte SARS-CoV-2-spezifische T-Zell-Immunantwort. Abbildung A zeigt die IL-2-Antwort und B die IFN-γ-Antwort. In C ist die kombinierte IL-2- und IFN-γ-Antworten dargestellt. Not reactive wurde nur gewertet wenn beide Immunantworten negativ waren. Die Entwicklung der SARS-CoV-2-Anti-Spike-IgG-Antikörper, bestimmt mit dem Abbott-Assay, sind in Abbildung D dargestellt, diejenigen mit dem GenID-Assay in Abbildung E. Die Kombination aus beide Antworten sind zusammengefasst in Abbildung F.
Waagerechte (gestrichelte) Linien zeigen die Cut-off Bereiche zwischen negativer und positiver humoraler Immunantwort (D und E), sowie zwischen negativ, borderline und positiver zellulärer Immunantwort (A und B) dar.

T1: 4 Wochen nach Grundimmunisierung
T2: 6 Wochen nach Grundimmunisierung

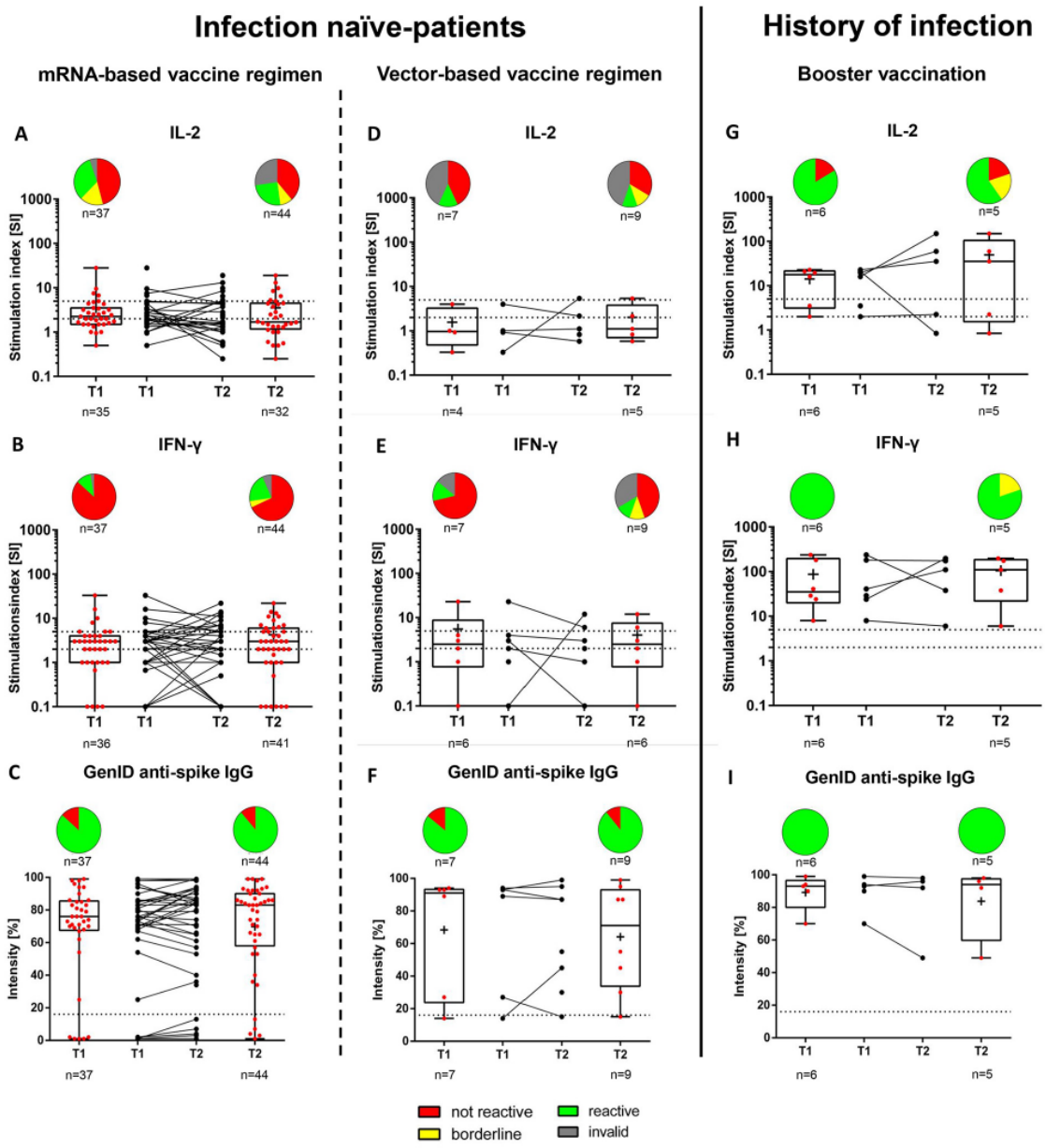


Abbildung 5: Dargestellt ist die T-Zell-spezifische Immunantwort aufgeteilt nach Patienten mit (History of Infection) und ohne (Infection naive Patients) durchgemachter COVID-19 Infektion. Abbildung A, D und G zeigen die IL-2-Immunantwort, B, E und H die IFN-γ-Immunntwort und Abbildung C, F und I zeigt die Entwicklung der SARS-CoV-2-Anti-Spike-IgG-Antikörper.

Waagerechte (gestrichelte) Linien zeigen die Cut-off Bereiche zwischen negativer und positiver humoraler Immunantwort (A, F und I), sowie zwischen negativ, borderline und positiver zellulärer Immunantwort (A,B,D, E, G und H)

Pt	Alter, Jahre	Geschlecht	Impfstoff	Grundkrankheit der Niereninsuffiizienz	Dialysedauer Dauer	BMI, kg/m²	Komorbiditäten	Aktuelle Immunsuppression	Total IgG at T1, g/l	Zelluläre Impfantwort
1	73	M	Pfizer/BioNTech BNT162b2	Multiples Myelom	17	26.5	keine	Cyclophosphamid, Bortezomib, und Prednisolon	6.3	negativ bei T1/T2
2	70	M	Pfizer/BioNTech BNT162b2	MPO-ANCA-positive Vasculitis	3	23.1	arterielle Hypertonie, Diabetes mellitus	Rituximab und Prednisolon	4	negativ bei T1/T2
3	58	W	Pfizer/BioNTech BNT162b2	MPO-ANCA-positive Vasculitis	32	43.4	arterielle Hypertonie, Diabetes mellitus	Rituximab und Prednisolon	6.2	positiv bei T1 negativ bei T2
4	57	W	Pfizer/BioNTech BNT162b2	kardiorenales Syndrom	3	24.4	Zn. Hodgkin Lymphom	keine	14.5	negativ bei T1/T2
5	57	M	Pfizer/BioNTech BNT162b2	diabetische Nephropathie	49	19.8	Inselzell-Transplantation	Tacrolimus, Mycophenolat mofetil und Prednisolon	7.4	negativ bei T1/T2

Tabelle 1: Charakteristika aller immunsupprimierten Patienten. Alle immunsupprimierte Patienten wiesen eine fehlende humorale Impfantwort auf. Die zelluläre Impfantwort auf die SARS-CoV-2-Impfstoffe zum Zeitpunkt T1 und T2 ist in der letzten Spalte dargestellt.
w: weiblich, m: männlich

Die beobachtete hohe humorale Immunantwort auf das SARS-CoV-2-Spike-Protein ist ähnlich wie bei einer kürzlich durchgeführten Impfstoffstudie mit gesunden Erwachsenen[141]. In einigen Studien zur humoralen Reaktion bei Hämodialysepatienten wurden ähnliche (> 90 %) Serokonversionsergebnisse berichtet[142-145], die vergleichsweise höher sind als in anderen Studien, in denen 77–82 % der Dialysepatienten positive Anti-Spike-IgG-Antikörperwerte aufwiesen[61,146-148]. Die beobachteten Unterschiede in der Serokonversionsrate zwischen den ausgewählten Studien können zum Teil auf die große Variation in der Anzahl der Dialysepatienten mit immunsuppressiver Therapie (0–12,0 %) oder mit einer Krebserkrankung in der Vorgeschichte (0–35,2 %) zurückzuführen sein, da beides anerkannte Risikofaktoren für eine verringerte Immunantwort nach der Impfung sind[61,146,147]. Vergleichbare Längsschnittdaten, die die Dynamik der humoralen Reaktion bei Dialysepatienten 4 Wochen und 6 Wochen nach der Impfung analysieren, liegen nicht vor. Eine Studiengruppe wies jedoch kürzlich darauf hin, dass die humorale Reaktion 6 Monate nach der SARS-CoV-2-Impfung bei Patienten mit MD abnimmt[149]. Ob der Antikörperverlust durch das geschwächte Immunsystem von Dialysepatienten oder durch die Impfstoffformen oder durch beides verursacht wird, bleibt unklar.

Neue Erkenntnisse deuten darauf hin, dass für einen wirksamen Schutz gegen SARS-CoV-2 sowohl eine antikörpervermittelte als auch eine T-Zell-vermittelte Immunität erforderlich ist[150]. Unsere Ergebnisse liefern jedoch Hinweise darauf, dass ein erheblicher Anteil der Patienten möglicherweise keine zelluläre Immunität entwickelt, obwohl fast alle Patienten Antikörper entwickelt haben. Unsere Ergebnisse stehen im Einklang mit früheren Studien bei Dialysepatienten, die eine unzureichende zelluläre Immunantwort nach der SARS-CoV-2-Impfung beschrieben, mit einer T-Zell-Aktivierung von 31–78 %[61,143,145], die im Vergleich zur Allgemeinbevölkerung (88,2 %)[151] niedriger, aber im Vergleich zu Nierentransplantatempfängern (5,1–35,0 %) höher ist[152,153]. Die unzureichende zelluläre Reaktion nach der SARS-CoV-2-Impfung bei Dialysepatienten stimmt mit der beeinträchtigten zellulären Reaktion überein, von der nach der Hepatitis-B-Virus-Impfung bei Hämodialysepatienten berichtet wurde[140]. Allerdings müssen die Ergebnisse der zellulären Immunantwort aus solchen Studien angesichts der unterschiedlichen Methoden zur Bestimmung der zellulären Imunantwort vorsichtig interpretiert werden.

Interessanterweise wurde beobachtet, dass Dialysepatienten, die nach einer SARS-CoV-2-Infektion eine Auffrischungsimpfung erhielten, eine deutlich bessere humorale und zelluläre Immunität im Vergleich zu SARS-CoV-2-naiven Patienten mit vollständiger Impfung aufwiesen[87]. Andere Studien deuteten ebenfalls darauf hin, dass eine vorherige Seropositivität bei Dialysepatienten vor einer SARS-CoV-2-Infektion zu schützen scheint[146,154]. Forbes et al.[155] berichteten, dass Hämodialysepatienten nach einer bestätigten COVID-19-Infektion eine robuste und anhaltende Antikörperreaktion aufweisen. Dort zeigten 71 % der Kohorte eine positive Reaktion 6 Monate nach der Impfung. Zusätzlich zeigt sich ein stetiger Anstieg der Konzentration der gebildeten Antikörper in dieser Gruppe. Der Grund für die stärkere humorale und zelluläre Immunantwort bei MD-Patienten nach einer natürlichen COVID-19-Infektion ist nicht bekannt, es wurden aber ähnliche Ergebnisse für immunkompetente Personen und Transplantatempfänger berichtet[61,154,155]. Es liegt nahe, dass das hohe Entzündungsniveau, das bei Dialysepatienten während der COVID-19-Infektion beobachtet wird, zu einer stärkeren antigenen Herausforderung und Lymphozytenrekrutierung beiträgt, was wiederum zu einer stärkeren zellulären und humoralen Immunantwort nach einer COVID-19-Infektion führt als bei der durch den Impfstoff vermittelten primären Immunantwort[87].

Unklar bleibt jedoch, ob der höhere Antikörperspiegel mit einem besseren Schutz gegen eine SARS-CoV-2-Infektion korreliert[156,157]. Unsere Daten zeigten, dass die höheren Werte von SARS-CoV-2-Anti-Spike-IgG zu beiden Zeitpunkten mit einer höheren Rate an zellulärer Immunität verbunden sind[87]. Daher vermuten wir, dass diese Patienten auch einen höheren Schutz gegen eine SARS-CoV-2-Infektion haben.

Nebenwirkungen der Impfung traten in bis zu 46,7 % der Fälle auf, waren aber in der Regel leicht (lokale Schmerzen und Schwellungen) und beschränkten sich meist (in 89,3 % der Fälle) auf die ersten 3 Tage nach der Impfung, was mit früheren Berichten übereinstimmt[143,158].

Eine große Stärke unserer Studie besteht darin, dass wir die humorale und die zelluläre Immunität verglichen haben, die bisher in der Literatur wenig Beachtung gefunden haben. Wir haben auch die zelluläre Immunität gemessen, einschließlich IL-2 und IFN-γ, was eine Bewertung sowohl der frühen als auch der späten zellulären Immunantwort ermöglicht[159] und in der Literatur bislang so noch nicht beschrieben worden ist.

Es lässt sich somit zunächst schlussfolgern, dass SARS-CoV-2-naive Patienten sehr wahrscheinlich von einer dritten Impfstoffinjektion profitieren, um die Immunogenität zu optimieren und den Schutz aufrechtzuerhalten, da sie im Gegensatz zu Patienten mit einer früheren COVID-19-Impfung nach einer Dosis eine deutlich reduzierte Impfantwort aufweisen.

2.2.2.3. Humorale und zelluläre Immunantwort nach Booster-Impfung mit dem mRNA-1273-SARS-CoV-2-Impfstoff bei Dialysepatienten

Diese Schlussfolgerung führte uns zur Folgestudie, in der wir in derselben Kohorte die Anti-SARS-CoV-2-Spike-Antikörper mit einem Dot-Plot-Array (GenID, Straßberg, Deutschland) und einem Chemilumineszenz-Mikropartikel-Immunoassay (Anti-S AdviseDx Anti-SARS-CoV-2-Spike-Antikörper II, Abbott, Chicago, IL, USA) sowie die zelluläre Impfantwort mittels des ELISpot-Assay, GenID) gemessen haben[88]. Die Immunantwort wurde 6 Monate (T3) nach der Grundimpfung (und vor der Auffrischungsimpfung) sowie 4 Wochen (T4) nach der Auffrischungsimpfung mit dem mRNA-basierten mRNA-1273-(Moderna-Biotech-)Impfstoff evaluiert[89].

Von der ursprünglichen Kohorte (n = 60) standen 47 Patienten (78,3 %) für eine Nachuntersuchung zur Verfügung (T3: n = 42; T4: n = 46; 5 Patienten wurden in andere Dialysezentren verlegt; 6 Patienten starben an nicht COVID-19-assoziierten Ursachen; 2 Patienten erhielten den Booster außerhalb ihres Dialysezentrums). 2 Patienten hatten trotz vollständiger Grundimmunisierung eine asymptomatische COVID-19-Durchbruchsinfektion und wurden daher erst zum Zeitpunkt T4 getestet. Die Ergebnisse der Testzeitpunkte T3 und T4 wurden mit den Ergebnissen zu den Zeitpunkten T1 und T2 (nach der Grundimmunisierung) verglichen. Die medianen anti-SARS-CoV-2-Spike-Antikörperspiegel (Abbott-Array) waren bei T3 signifikant niedriger als bei T2 (501 [Interquartilsbereich, 134-1703] vs. 2240 [756-7687] AU/ml; P < 0,001) und stiegen nach der Auffrischungsimpfung deutlich auf 40.000 [6855-40.000] AU/ml an (P < 0,001). Beim prozentualen Positivitätsstatus wurden zwischen T2 und T4 keine Veränderungen beobachtet (Abb. 6 A–C).

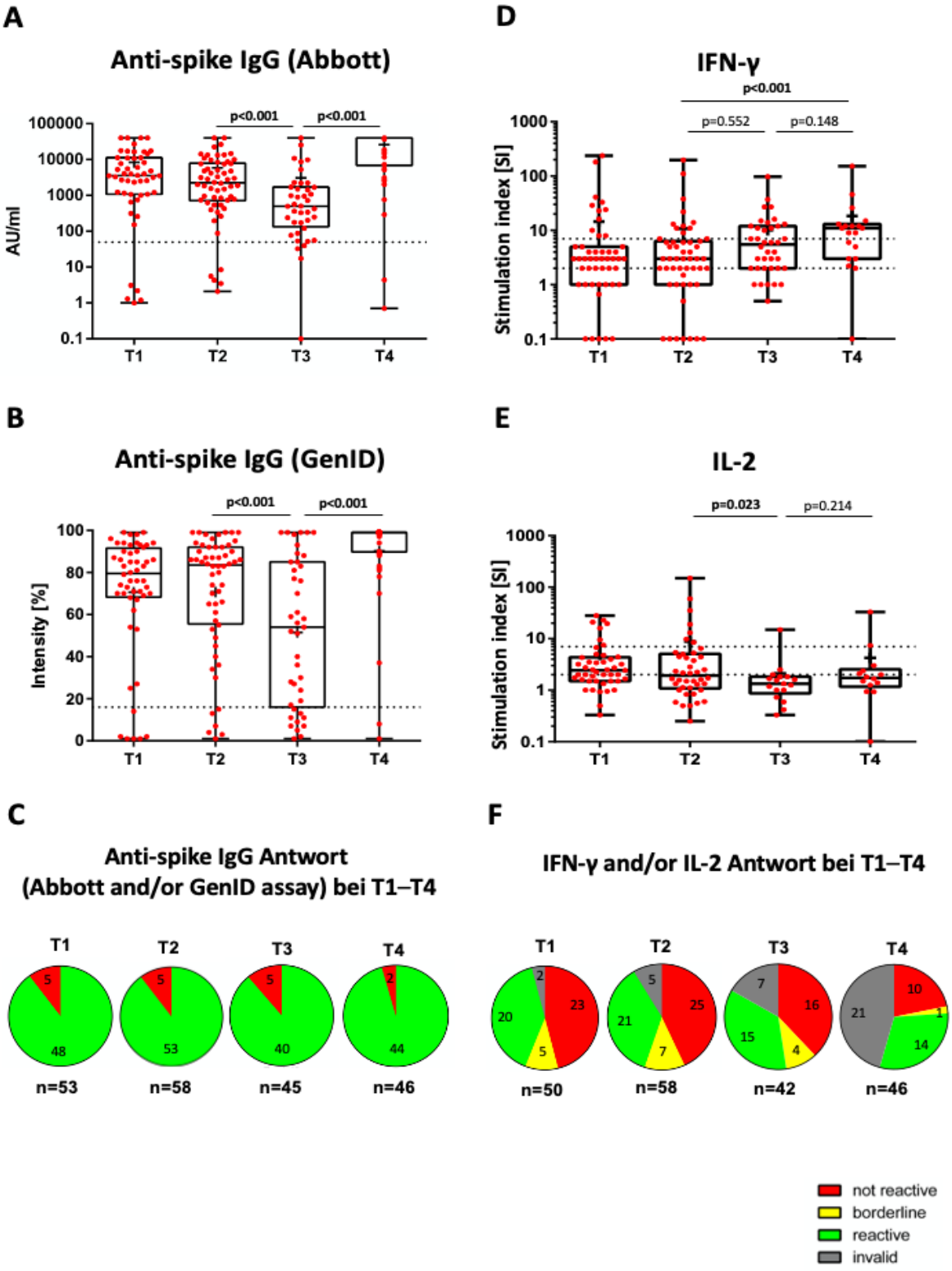


Abbildung 6: Dargestellt ist die T- und B-Zell-spezifische Immunantwort. Abbildung A, B und C zeigt die Entwicklung der SARS-CoV-2-Anti-Spike-IgG-Antikörper, Abbildung D die Entwicklung der T-Zell-spezifischen IFN-γ- und E die IL-2-Antwort. In F ist die kombinierte Immunantwort von IFN-γ und/oder IL-2 dargestellt. Not reactive wurde nur gewertet, wenn beide Immunantworten negativ waren. Reactive wurde gewertet, wenn beide Immunantworten als reactive beschrieben wurden. Als Borderline wurden die Ergebnisse gewertet, wenn mindestens eine der beiden Immunantworten borderline war, oder beide Immunantworten weder negativ noch positiv waren.

Waagerechte (gestrichelte) Linien zeigen die Cut-off Bereiche zwischen negativer und positiver humoraler Immunantwort (A und B), sowie zwischen negativ, borderline und positiver zellulärer Immunantwort (D und E) dar.

Der mediane IL-2-Stimulationsindex (SI) war bei T3 niedriger als bei T2 (P = 0,023), nicht aber der IFN-γ-SI (P = 0,552) zwischen beiden Zeitpunkten (Abb. 6D–E). Bemerkenswert ist, dass die IFN-γ-SI-Spiegel bei T4 höher waren als bei T2 (P<0,001). Beim Vergleich des prozentualen Reaktivitätsmusters der IFN-γ- und/oder IL-2-ELISpot-Assays zwischen T2 und T4 wurden keine Veränderungen beobachtet (Abb. 6F).

Der GenID-Assay zeigte, dass Patienten mit IFN-γ-produzierenden T-Zellen bei T3 höhere Anti-SARS-CoV-2-Spike-Antikörperspiegel aufwiesen (P = 0,028, n = 30), nicht aber der Abbott-Array (P = 0,08; n = 28). Bei T4 gab es keinen signifikanten Unterschied für beide Assays (Abbott-Array: P = 0,51, n = 17; GenID-Assay: P = 0,442, n = 17). IL-2 konnte aufgrund der geringen Anzahl auf der reaktiven Seite bei T3 (n = 1) und T4 (n = 3) nicht analysiert werden.

Patienten mit einer COVID-19-Anamnese wiesen im Vergleich zu infektionsfreien Patienten bei T2 (n = 5 bzw. 53, Gesamtzahl = 58) und T3 (n = 5 bzw. 35, Gesamtzahl = 40) anhaltend höhere Anti-SARS-CoV-2-Spike-Antikörperspiegel auf[89]. Bemerkenswert war, dass die Booster-Impfung in beiden Gruppen bei T4 mittlere IgG-Werte bis zur oberen Nachweisgrenze von 40.000 AU/ml ergab[89]. Die zelluläre Immunantwort war bei Patienten mit einer COVID-19-Anamnese höher im Bereich der SARS-CoV-2-spezifischen IFN-γ-Spiegel bei T2 (P < 0,001), aber nicht in der IL-2-Antwort (P = 0,07). Bei den IFN-γ-SI-Spiegeln bei T3 (P = 0,252) und T4 (P = 0,299) wurden keine Unterschiede zwischen beiden Gruppen festgestellt. Man muss hier jedoch einschränkend erwähnen, dass aufgrund der hohen Anzahl ungültiger Proben (Hämolyse bei zu kalter Umgebungstemperatur beim Transport) von Patienten mit COVID-19-Anamnese die IL-2-Immunantworten zu T3 und T4 nicht analysiert werden konnten.

Somit deutet die Dynamik der Immunantwort 4 Wochen nach dem mRNA-1273-SARS-CoV-2-Impfstoff-Booster auf eine robuste humorale Immunantwort 6 Monate nach der Grundimpfung hin (> 90 %), was mit früheren Berichten übereinstimmt, die Hämodialysepatienten und gesunde Kontrollpersonen einschlossen[160,161]. Die Grundimpfung führte zwar zu ausgesprochen hohen Anti-SARS-CoV-2-Spike-Antikörperspiegeln (am höchsten bei Patienten mit durchgemachter COVID-19-Infektion[87]), aber die humorale Reaktion ließ innerhalb von 6 Monaten deutlich nach[87]. Die durch handelsübliche Tests definierte IgG-Seropositivität überschätzt möglicherweise die tatsächliche Wirksamkeit der durch den Impfstoff induzierten

humoralen Immunität, da der Grenzwert, der mit dem Schutz vor einer SARS-CoV-2-Infektion korreliert, unbekannt ist. Im Gegensatz dazu beobachteten wir eine anhaltende relativ schwache zelluläre Immunreaktion nach der Auffrischungsimpfung (zelluläre Impfantwort lediglich bei 51,7 % der Patienten), obwohl die IFN-γ-SI-Werte bei den Patienten mit zellulärer Impfantwort deutlich anstiegen[89]. In Übereinstimmung mit früheren Arbeiten[161] ist das Vorhandensein von Antikörpern daher möglicherweise nicht automatisch mit einer funktionellen zellulären Immunität verbunden, die wahrscheinlich eine wichtige Komponente für den langfristigen Schutz gegen SARS-CoV-2 ist. Sowohl wir als auch andere Autoren haben bereits gezeigt, dass die Zytokininduktion während der primären Immunantwort mit einer bevorzugten Induktion von IL-2-produzierenden T-Zellen einhergeht[87], während Reaktivierungen wie bei BCG- Infektionen mit IFN-produzierenden T-Zellen, verbunden sind[162]. Letzteres könnte auch auf Auffrischungsimpfungen zutreffen, wie in der vorliegenden Studie gezeigt wurde. Insgesamt lassen unsere Daten auf eine fortschreitende Abnahme der humoralen Immunität und eine anhaltend relativ schwache zelluläre Immunantwort innerhalb von 6 Monaten schließen. Ebenso konnte gezeigt werden, dass die Auffrischungsimpfung in der Lage ist, die humorale Immunität wieder deutlich zu erhöhen. Wir gehen außerdem davon aus, dass das Auftreten von SARS-CoV-2-Varianten mit hohem Potenzial zur Immunevasion bei Dialysepatienten eine Auffrischungsimpfung 4–6 Monate nach der Grundimpfung erforderlich machen könnte[89].

3. ZUSAMMENFASSUNG UND AUSBLICK

Die vorliegende kumulative Habilitationsschrift befasst sich mit den aktuellen Herausforderungen in der Behandlung der chronischen Niereninsuffizienz. Das Hauptaugenmerk liegt auf neurokognitiven und immunologischen Aspekten. Es werden verschiedene bisher vielleicht wenig beachtete Zusammenhänge zwischen Einschränkungen der kognitiven Leistungsfähigkeit und chronischer Niereninsuffizienz, mögliche neue Ansätze und Optionen der Nierentransplantation und nicht zuletzt die Entwicklung der humoralen und zellulären Immunität bei der SARS-CoV-2 Erkrankung auf die neu zugelassenen Impfstoffe untersucht.

Kognitive Einschränkungen sind ein wenig beachtetes, aber häufiges Phänomen bei Dialysepatienten[20,25]. In unserer Studie konnten wir nachweisen, dass 75 % der Patienten unter kognitiven Beeinträchtigungen litten. Bei den Patienten mit einer kognitiven Beeinträchtigung waren alle kognitiven Bereiche betroffen, wobei Depression und niedriger Bildungsgrad einen signifikanten negativen Einfluss auf die Stärke der kognitiven Leistungsfähigkeit aufweisen[64] (A1). Die stärkste Beeinträchtigung der kognitiven Leistung wurde beim unmittelbaren Gedächtnisabruf, die beste Leistung beim Benennen festgestellt. Interessanterweise wurde kein weiterer signifikanter Abfall der kognitiven Leistungsfähigkeit nach einem Follow-up von 1 Jahr in irgendeinem Bereich beobachtet (A1)[64]. Die Erstellung eines neurokognitiven Profils ist hilfreich und wichtig, da die Prävalenz von kognitiven Beeinträchtigungen bei Hämodialysepatienten hoch ist. Da Depressionen einen signifikanten Einfluss auf kognitive Beeinträchtigungen haben, ist eine frühzeitige Erkennung unerlässlich, um eine Behandlung in einem frühen Stadium einzuleiten und die kognitive Leistung positiv zu beeinflussen.

Wichtig war uns die Erkenntnis, dass der Zeitpunkt der Untersuchungen für die kognitive Leistungsfähigkeit keine Rolle spielt (A2)[68]. In unserer Studie konnten wir zeigen, dass der Testzeitpunkt (erste 2 Stunden unter Hämodialyse vs. letzte 2 Stunden unter Hämodialyse vs. hämodialysefreier Tag) keinen Einfluss auf die kognitive Funktion bei Hämodialysepatienten in Routineindikationen hat. Dies hat insbesondere deshalb klinische Relevanz, da die kognitiven Tests als ein Element der Routineuntersuchung von Dialysepatienten während der Visite eingesetzt werden können. Dies gibt uns einen Überblick über die kognitive Funktion der Patienten und

kann auch als Verlaufsparameter genutzt werden, um eine mögliche Verschlechterung der kognitiven Funktion frühzeitig zu erkennen.

Im Wissen um die kognitiven Beeinträchtigungen bei Dialysepatienten war das Ziel der Folgestudie, das Ausmaß der kognitiven Beeinträchtigung vor und nach der Transplantation zu untersuchen und mit Hilfe von standardisierten neurokognitiven Tests ein eindeutiges Profil der kognitiven Funktion bei Patienten vor und nach der Transplantation zu erstellen. Es sollte außerdem untersucht werden, ob die Verbesserung der Nierenfunktion nach einer Transplantation zu einer Verbesserung der kognitiven Leistungsfähigkeit führt (A3)[76].

Die Ergebnisse unserer derzeit in Rekrutierung befindlichen Studie könnten potenziell wichtige Auswirkungen auf die Prävention und Behandlung kognitiver Beeinträchtigungen bei nierentransplantierten Personen haben. Durch neue Erkenntnisse über das neurokognitive Profil und die Zuordnung der entsprechenden Defizite könnte es möglich sein, ein individualisiertes Trainingsprogramm zu erstellen, um die kognitiven Defizite bei diesen Personen positiv zu beeinflussen (A3).

Daneben besteht eine große Herausforderung der Transplantationsnephrologie darin, dem stetig wachsenden Organmangel entgegenzuwirken. Die Nierentransplantation ist nach wie vor die bevorzugte Therapie für Patienten mit terminaler Niereninsuffizienz. Ihr sind jedoch durch den Mangel an Nierenspenden Grenzen gesetzt. Obwohl ein hoher Prozentsatz der Patienten mit funktionierenden Transplantaten stirbt[77-79], können viele von ihnen leider nicht als Organspender in Betracht gezogen werden. Die Gründe dafür sind vielfältig.

Eine neue Option, um den Pool an Nierenspendern zu erhöhen, wäre die Spende einer zuvor transplantierten Niere an einen neuen Empfänger. Diese Möglichkeit hat bisher wenig Beachtung gefunden und ist entsprechend nur selten durchgeführt worden. Unsere Untersuchung konnte jedoch zeigen, dass die Retransplantation eines Nierentransplantats erfolgreich durchgeführt werden kann, selbst wenn die erste Transplantation lange zurückliegt (A4)[86]. Allerdings scheint eine sorgfältige Prüfung der Daten der Spender (Erst- und Zweitspender) erforderlich zu sein, um eine schwere chronische Schädigung auszuschließen. Das Potenzial zur Durchführung solcher Retransplantationen ist aus unserer Sicht noch nicht voll ausgeschöpft. Es sollten daher Anstrengungen unternommen werden, auch solche Spenden in Betracht zu ziehen, und zwar sowohl in den Spenderzentren, um auf ihr Potenzial aufmerksam zu machen, als auch in den Transplantationszentren, um die Akzeptanz dieser

Transplantate nach sorgfältiger Prüfung zu erhöhen (A4)[86]. Es muss jedoch auch klar sein, dass die oben genannten Punkte aufgrund der geringen Fallzahlen nur zusätzlich zu den anderen vielschichtigen Ansätzen in Betracht gezogen werden können.

Im Rahmen der COVID-19-Pandemie wurde schnell bekannt, dass Patienten mit terminaler Niereninsuffizienz aufgrund ihres herabgesetzten Immunsystems und der Komorbiditäten ein deutlich erhöhtes Risiko für die Entwicklung eines schweren Verlaufes einer SARS-CoV-2-Erkrankung haben[53-55]. Die Entwicklung und Zulassung neuer Impfstoffe hat in der Normalbevölkerung zu einer robusten Impfantwort geführt[14,15]. Da Dialysepatienten jedoch zum einen durch die Niereninsuffizienz per se und zum anderen durch die Einnahme von z.B. immunsuppressiven Medikamenten mit hoher Wahrscheinlichkeit eine schwächere Immunantwort entwickeln, führten wir Studien zur Messung der humoralen und zellulären Immunität nach der Impfung gegen SARS-CoV-2 durch. Valide Daten waren bis dato für unser Patientenkollektiv noch nicht verfügbar. Die SARS-CoV-2-spezifische zelluläre Immunantwort wurde mit IFN-γ- und IL-2-ELISpot-Assays und die humorale Immunantwort mit einem Dot-Plot-Array und einem chemilumineszenten Mikropartikel-Immunoassay bewertet (A5) [88].

Bei der Mehrheit der Dialysepatienten, die geimpft wurden, kam es nach einer Einzeldosis oder einer homologen Zweifachdosis-Impfung zur Entwicklung von Anti-Spike-IgG-Antikörpern gegen SARS-CoV-2, die jedoch 6 Wochen nach der vollständigen Immunisierung schnell abnahmen (A6)[87]. Nur etwa 50 % der Patienten entwickelten eine T-Zell-Immunität[87]. Wichtig ist außerdem, dass eine hohe Anti-Spike-IgG-Antikörperantwort mit einer besseren zellulären Immunität assoziiert war und dass die Immunantwort bei Patienten mit durchgemachter COVID-19-Erkrankung deutlich stärker war (A6)[87]. Als Schlussfolgerung kann postuliert werden, dass sowohl SARS-CoV-2-naive Dialysepatienten, aber auch Patienten mit durchgemachter COVID-19-Erkrankung von einer dritten Impfstoffinjektion (Booster-Impfung) profitieren können, um die Immunogenität zu optimieren und den Schutz aufrechtzuerhalten (A5)[87].

Den Effekt einer solchen Booster-Impfung untersuchten wir in unserer Folgestudie beim selben Patientenkollektiv 6 Monate nach der Grundimmunisierung. Die Immunantwort wurde vor und nach der Auffrischungsimpfung mit dem mRNA-basierten mRNA-1273-(Moderna-Biotech-)Impfstoff getestet (A7)[89]. Insgesamt deuten unsere Daten auf eine fortschreitende Abnahme der humoralen Immunität und eine anhaltend relativ schwache zelluläre Immunantwort innerhalb von 6 Monaten hin. Die Auffrischungsimpfung ist jedoch geeignet, die humorale Immunität wieder deutlich zu

erhöhen[89]. Wir vermuten, dass das Auftreten von SARS-CoV-2-Varianten mit hohem Potenzial zur Immunevasion bei Dialysepatienten eine Auffrischungsimpfung 4–6 Monate nach der Grundimpfung erforderlich machen könnte.

Mit Hilfe der bisher erzielten Wissensfortschritte bezüglich der kognitiven Leistungsfähigkeit, Transplantationsmedizin und der Impfansätze bei SARS-CoV2-Erkrankungen bei Patienten mit chronischer Niereninsuffizienz kann es gelingen, die aktuellen Herausforderungen in der Behandlung der chronischen Niereninsuffizienz für unsere Patienten in Zukunft besser zu meistern.

4. EIGENE ORIGINALARBEITEN

4.1. ASSESSMENT OF COGNITIVE IMPAIRMENT AND RELATED RISK FACTORS IN HEMODIALYSIS PATIENTS (A1)

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Kognitive Beeinträchtigungen bei Hämodialysepatienten sind in den letzten Jahren immer mehr bekannt geworden und wurden bei bis zu 80 % der Patienten festgestellt. Alter, eine hohe Prävalenz von kardiovaskulären Risikofaktoren wie Schlaganfall und TIA, Urämie und multiple Stoffwechselstörungen sind die häufigsten Einflussfaktoren bezüglich kognitiver Beeinträchtigungen bei Hämodialysepatienten. Wir haben eine prospektive Studie an 408 Patienten aus 10 Hämodialysezentren in Region Mittelhessen (Deutschland) durchgeführt. Diese Patienten wurden einer CERAD-Testbatterie unterzogen, die aus 5 Tests besteht, um das kognitive Profil zu beurteilen. Je nach Grad der Beeinträchtigung und der Anzahl der Bereiche, in denen das Defizit festgestellt wurde, wurden die Patienten als leicht, mäßig oder schwer beeinträchtigt eingestuft. Es wurde ein kognitives Profil erstellt und die Veränderung der Leistung im Laufe der Zeit bei Hämodialysepatienten basierend auf ihrem kognitiven Ausgangsstatus (Ausgangswert vs. 1 Jahr Follow-up) untersucht.

Von insgesamt 479 in Frage kommenden Patienten absolvierten 408 Patienten zu Beginn der Studie alle Tests. Nur 25 % (n = 102) der Patienten waren kognitiv gesund. 14 % (n = 57), 36,5 % (n = 149) und 24,5 % (n = 100) der Patienten wiesen eine leichte, mittlere bzw. schwere Beeinträchtigung auf. Bei den Patienten mit einer kognitiven Beeinträchtigung waren alle kognitiven Bereiche betroffen, wobei Depression und Bildung signifikant mit dem Grad der Beeinträchtigung assoziiert waren. Die stärkste Beeinträchtigung der kognitiven Leistung wurde beim direkten Gedächtnisabruf und die beste Leistung beim Benennen festgestellt. Signifikante Veränderungen der kognitiven Leistungsfähigkeit wurden nach 1 Jahr nicht beobachtet.

Unsere Studie zeigte, dass die Prävalenz kognitiver Beeinträchtigungen bei Hämodialysepatienten hoch ist. Sie wird durch das Vorliegen einer Depression beeinflusst, darüber hinaus haben Bildung und Depressionen einen Einfluss auf die kognitiven Testergebnisse. Eine frühzeitige Erkennung ist daher unerlässlich, um eine Behandlung in einem frühen Stadium einzuleiten und die kognitiven Leistungen positiv zu beeinflussen.

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ORIGINAL ARTICLE

Assessment of cognitive impairment and related risk factors in hemodialysis patients

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Abstract

Background Cognitive impairment in hemodialysis patients has been acknowledged over the last years and has been reported in up to 80% of patients. Older age, high prevalence of cardiovascular risk factors, such as stroke and transient ischemic attack, uremia, and multiple metabolic disturbances represent the most common factors for cognitive impairment in hemodialysis patients.

Methods We conducted a prospective cohort study on 408 patients from 10 hemodialysis centers in the regional government district of Middle Hesse (Germany). Patients underwent a neuropsychological test battery consisting of five tests, in addition to a phonemic fluency test, to assess cognitive profile. The patients were classified as no cognitive impairment or mildly-, moderately- or severely-impaired cognitive function, depending on the degree of impairment and number of domains where the deficit was determined. We analyzed the cognitive profile and the change in performance over time in hemodialysis patients based on their cognitive status at baseline vs. 1-year follow-up.

Results Of 479 eligible patients, 408 completed all tests at baseline. Only 25% (n = 102) of the patients had no cognitive impairment. Fourteen per cent (n = 57), 36.5% (n = 149), and 24.5% (n = 100) of patients showed mild, moderate, and severe impairment, respectively. In patients with cognitive impairment, all cognitive domains were affected, and impairment was significantly associated with depression and education. The most impaired cognitive performance was immediate memory recall, and the best performance was found in naming ability. No significant change was observed after 1-year follow up in any domain.

Conclusion Our study shows that the prevalence of cognitive impairment in hemodialysis patients is high and that it is affected by the presence of depression. Furthermore, education has an effect on cognitive test results. As depression has a significant influence on cognitive impairment, its early identification is essential in order to initiate treatment at an early stage, hoping to positively influence cognitive performance.

Keywords Cognitive Impairment · CERAD · Hemodialysis · Depression · Cognitive decline

Abbreviations

CERAD	Consortium to establish a registry for Alzheimer's disease
CKD	Chronic kidney disease
cp	Constructive praxis
der	Delayed recall
dr	Immediate recall
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
GDS	Geriatric depression scale
MMSE	Mini-mental-state-examination
MoCA	Montreal cognitive assessment
mr	Memory recognition
na	Naming
pf	Phonemic fluency

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SBI	Silent brain infarcts
sf	Semantic fluency
TIA	Transient ischemic attack

Introduction

The association of cognitive impairment with chronic kidney disease (CKD) has been reported over the last decade [1–4]. Several studies have suggested that the prevalence of cognitive impairment in patients with CKD, especially in end stage renal disease (ESRD), is up to 80% [1, 2, 5–8], but detailed data regarding different domains of cognitive functions, especially in patients with mild cognitive impairment, is scarce in literature. Early detection of cognitive impairment is of paramount significance in order to take preventive action, to assess illness-related grief, and to avoid misunderstandings during medical care [9]. Different types of dementia show different cognitive profiles. In addition to Alzheimer's disease, where memory disorders (especially retention) dominate, vascular dementia represents one of the most common types of dementia associated with impairment in executive and parts of memory function, such as immediate recall, but not retention [10].

Hemodialysis patients are at increased risk of cognitive impairment because of their old age, high prevalence of cardiovascular risk factors, cerebrovascular involvement, including stroke and transient ischemic attack (TIA), and multiple metabolic disturbances [11–13]. Anemia has also been associated with poor cognitive function and dementia [14, 15].

Hemodialysis patients seem to suffer mostly from impairment of executive functions. Recent studies have reported associated vascular risk factors [1, 2]. Most of these studies used either the frequently applied Mini-Mental-Status-Examination (MMSE) or very heterogeneous scales. The MMSE, which is designed as a screening instrument and not as a diagnostic one, focuses on orientation, memory and language, and is, therefore, not an appropriate tool for detecting different disease-related cognitive impairments. Detailed test batteries are often time-consuming and require different standardization for each task. Therefore, a within-subject comparison in relation to performance in different cognitive domains seems to be highly required. In addition, data concerning the temporal development of cognitive impairment in hemodialysis patients are scarce, and furthermore, it remains unclear which factors might influence the development of cognitive impairment in these patients.

The goal of our study was to examine the extent of cognitive impairment, and to derive a distinct profile of cognitive function in hemodialysis patients using a standard tool for neuropsychological assessment, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), in patients with mild cognitive impairment (MMSE Score ≥ 24). Furthermore, we explored a set of risk factors for deficits in cognitive performance as well as for its development.

Methods

We conducted a prospective cohort study in the regional government district of Middle Hesse (Germany) at 10 outpatient dialysis centers. Inclusion criteria were: at least 18 years of age, native German speaker and receiving hemodialysis three times per week. Patients under the legal supervision of a caretaker were excluded from the study.

Neuropsychological assessment

We applied the widely used CERAD test battery, consisting of five tests (semantic fluency, naming, verbal memory with the immediate, delayed and recognition recall subtests, constructional memory and constructional praxis) and a test of phonemic fluency, now included in the CERAD-Plus. The raw scores were transformed into z-scores using the same norm sample for all tests adjusted for age, sex and years of education.

Impairment was stratified using the algorithm adopted by Murray and colleagues [1] based on the Mayo criteria for mild cognitive impairment [16] and the Diagnostic and Statistical Manual, third Edition, Revised criteria for dementia as approximate guidelines [17]. Patients were classified depending on the amount of impairment and the number of domains the deficit was found in. Unimpaired patients performed better than 1.5 standard deviations (SD) below the norm sample in any test considered for the classification. Mildly impaired patients showed mild deficits (scores 1.50 to 1.99 SD below the norm sample) in only one domain, moderately impaired patients showed deficits in two domains or a severe deficit (2.0 SD below the norm sample) in one domain. Patients showing severe deficits in at least two domains were classified as severely impaired. The domains of executive functions (semantic and phonemic fluency), verbal memory (immediate and delayed recall), constructive praxis and language/naming were considered in the classification. As the performance in figural memory is related to the constructive skills, we did not consider the test in the classification of the patients or in further analyses. To evaluate the relationship between medical parameters and cognitive performance in general we built the CERAD-Score suggested by Chandler et al. [18]. The score combines the raw scores of the semantic fluency (limited to a maximum of 24 points), naming, immediate and delayed recall of a word list, recognition of those words and constructive praxis subtests, resulting in a total-score ranging from zero to one hundred points.

Dialysis measures, comorbidity, laboratory parameters

Data concerning hemoglobin, creatinine, calcium, phosphorus, albumin, triglycerides, cholesterol and urea, as well as pH-value, CO_2, bicarbonate, blood pressure, and dialysis dose were obtained. Demographic, comorbidity and current medication data were obtained from the medical records or were self-reported. The examinations, which took place within the first 90 min of dialysis therapy, were carried out by thoroughly instructed medical students.

Statistical methods

Demographic and medical parameters were compared among hemodialysis patients with no impairment, an impairment in any domain, or a severe impairment, using *t*-tests for normally distributed variables, Mann–Whitney-U-Tests for not normally distributed variables and Fisher's exact- or Cramer's-V Tests for categorical variables. We analyzed the correlation between different demographic, clinical, and laboratory parameters, including dialysis duration, dialysis efficiency (estimated by the Kt/V equation), and calcium-phosphate-product, and performance in different cognitive tests (Table S1). Parameters which showed statistically significant correlations with performance at different cognitive tests ($p < 0.05$) were entered as possible predictors in a multivariate regression model with a backward elimination method to test for an independent association. Predictors with *p-value* < 0.10 were considered significant and were retained in the model, while others were excluded. We performed the analysis of variance (ANOVA) test with repeated-measures to analyze the cognitive profile and the change in performance over time in hemodialysis patients based on the cognitive status at baseline. The inner-subject factors *time* (baseline vs. 1-year-Follow-up) and *test* (semantic fluency, phonemic fluency, naming, memory immediate recall, memory delayed recall, memory recognition, constructive praxis), as well as the between-subject factor *cognitive impairment* (none, mild, moderate, severe at baseline) resulted in a $2 \times 7 \times 4$ design with pairwise comparisons and planed contrasts for a priori analysis, choosing z-scores in immediate recall as reference. To explore the effect of depression on the decrease in cognitive performance, we calculated a 2×2 design (*time* × *depression*). The same analyses were repeated with the last observation carried forward method. All assumptions regarding multivariate regression analyses or variance analyses with repeated measures, including homoscedasticity, linearity, autocorrelation, normally distributed errors or dependent variable, multicollinearity and sphericity were accounted for by means of the appropriate methods. The Greenhouse-Geißer correction was used when the assumption of sphericity was violated. Differences were considered statistically significant at *p* values < 0.05. All analyses were performed using the Predictive Analysis SoftWare (PASW®) version 17.0 (SPSS Inc., Chicago, IL, USA) (Table 1).

Results

Patient characteristics

Out of 629 screened patients, 153 did not fulfill the inclusion criteria. Seventy eligible patients either refused (n = 67) or were not able to complete the neuropsychological testing (n = 3). Those patients had significantly fewer years of education, lower scores in the MMSE, higher diastolic blood pressure, higher values of hemoglobin and bicarbonate, relatively more coronary heart diseases, and lower smoking index. One hundred sixty-five patients were lost to follow-up. There were no significant differences in demographic or medical parameters at baseline between the excluded or attrited patients and those who completed the study, except for a higher prevalence of atrial fibrillation in excluded or attritted patients. No difference was found at baseline regarding test performance between the patients who completed the study and those who were lost to follow up.

Patients in the study group (n = 408) were on average 71.6 years (SD: 10.29) old at baseline and had a mean of 11.1 years (SD: 2.39) of education (school and professional education in total). Forty point two% of them were women, and the mean time on dialysis was 48.4 months (SD: 77.04). Thirty nine point eight% had diabetes; most of the patients were suffering from arterial hypertension (78.7%), 11.5% had a history of stroke or TIA and 8.3% had a diagnosis of depression.

Cognitive impairment

Only 25% (n = 102) of the patients were cognitively unimpaired. Fourteen percent (n = 57) had mild, 36.5% (n = 149) moderate and 24.5% (n = 100) severe impairment. Table 2 shows the frequency of cognitive impairment in the different tasks. The most prevalent impairment appeared in immediate memory recall as well as in phonemic and semantic fluency.

Non-dialysis specific factors and their association with cognitive test performance

In Table 1 the patients' characteristics are listed separately for the groups of; no cognitive impairment, at least mild deficits in any considered tests, and severe cognitive

Table 1 Characteristics and group differences between patients with and without cognitive impairment

Variable	No cognitive impairment	Cognitive impairment in any domain	Sig[1]	Severe cognitive impairment	Sig[2]
Age, mean ± sd (N)	71.6 ± 10.2 (102)	71.7 ± 9.8 (306)	.920	69.8 ± 9.0 (100)	.198
Female, % (N)	32.4% (33)	42.8% (131)	.063	44.0% (44)	.111
Years of education, mean ± SD (N)	11.5 ± 2.4 (102)	10.9 ± 2.3 (305)	**.029***	11.1 ± 2.3 (100)	.197
Time on dialysis, Months, mean ± SD (N)	36.97 ± 38.66 (73)	48.63 ± 56.37 (266)	.174	49.41 ± 47.63 (70)	.100
Hours on dialysis per session, mean ± SD (N)	4.2 ± 0.8 (102)	4.3 ± 0.5 (305)	.497	4.3 ± 0.5 (100)	.519
Primary Cause of ESRD, % (N)			.879		.734
Diabetes	26.5% (27)	23.9% (73)		21.0% (21)	
Vascular	11.8 (12)	12.7% (39)		11.0 (11)	
Others	60.8 (62)	61.1% (187)		63.0% (63)	
Systolic Blood pressure, mean ± SD (N)	129.4 ± 23.2 (89)	133.1 ± 20.0 (259)	.156	134.6 ± 21.1 (83)	.137
Diastolic Blood pressure, mean ± SD (N)	65.7 ± 12.0 (89)	67.0 ± 11.9 (258)	.387	68.0 ± 12.3 (82)	.254
Pulse pressure, mean ± SD	63.7 ± 18.3 (89)	66.1 ± 17.7 (258)	.279	66.7 ± 17.1 (82)	.281
Equilibrated Kt/v, mean ± SD (N)	1.5 ± 0.4 (87)	1.6 ± 0.5 (255)	.279	1.6 ± .5 (89)	.291
Hemoglobin, mean. ± SD (N)	11.6 ± 1.3 (102)	11.6 ± 1.2 (294)	.951	11.8 ± 1.2 (94)	.316
Albumin, mean ± SD (N)	36.6 ± 5.5 (88)	36.1 ± 5.1 (263)	.395	36.3 ± 4.7 (84)	.500
Calcium phosphate product, mean ± SD (N)	3.5 ± 1.1 (101)	3.8 ± 1.3 (296)	.183	3.9 ± 1.2 (94)	**.049***
Bicarbonate, mean ± SD (N)	22.3 ± 3.6 (84)	22.6 ± 3.2 (251)	.630	22.2 ± 2.9 (71)	.892
Arterial hypertension, % (N)	75.5% (77)	79.7% (244)	.188	81.0% (81)	.100
Cholesterol, mean ± SD (N)	173.5 ± 43.1 (80)	180.0 ± 98.6 (220)	.802	180.3 ± 45.8 (70)	.343
Coronary heart disease, % (N)	47.1% (48)	34.3% (105)	**.044***	32.0% (32)	.060
Diabetes mellitus, % (N)	37.3% (38)	39.2% (120)	.639	39.0% (39)	.660
Stroke or TIA, % (N)	10.8% (11)	11.8% (36)	.859	13.0% (13)	.664
Atrial fibrilation, % (N)	19.6% (20)	18.6% (57)	1.0	13.0% (13)	.340
Nicotine use, % (N)	38.2% (39)	31.7% (97)	.275	27.0% (27)	.102
Alcohol use, % (N)	5.9% (6)	4.9% (15)	.575	6.0% (6)	.501
MMSE. mean ± SD (N)	28.2 ± 1.6 (102)	27.4 ± 1.8 (306)	**.001****	26.9 ± 1.9 (100)	**.001****
None CI (28–30) % (N)	72.5% (74)	50.3% (154)		44.0% (44)	
Mild CI (25–27) % (N)	25.5% (26)	42.2% (129)		41.0% (41)	
Moderate CI (20–24) % (N)	2.0% (2)	7.5% (23)		15.0% (15)	
CERAD Score, % (N)	77.7 ± 7.9 (102)	64.4 ± 10.0 (306)	**.001****	59.6 ± 9.5 (79)	**.001****
Dementia, % (N)	0% (0)	0.7% (2)	.550	0.0% (0)	
Depression, % (N)	3.9% (4)	9.8% (30)	.064	10.0% (10)	.096

Bold print significance level *$p < .05$; **$p < .01$; ***$p < .001$

SD = standard deviation; [1]Comparison between patients with non cognitive impairment and those with mild cognitive impairment, [2] Comparison between patients with no cognitive impairment and those with severe cognitive impairment

impairment. Patients with no cognitive impairment had significantly more years of education and higher prevalence of coronary heart disease compared to those with mild cognitive impairment. Furthermore, female gender and depression tended to be more frequent in the group with mild cognitive impairment compared to the cognitively sound group (p = 0.063, 0.064, respectively). Compared to patients with severe cognitive impairment, cognitively unimpaired patients showed a significantly lower calcium phosphate product (0.049). Interestingly, dialysis duration (months) did not differ among the three groups (p = NS).

Multivariate regression analysis was conducted to investigate an independent association between age, gender, years of education, hemoglobin level, smoking (pack-year), stroke/TIA, depression, or hypertension and performance in different aspects of cognitive tests (Table 3).

Age showed, as expected, an independent negative association with semantic fluency, early and late memory recall, naming ability, constructive praxis, and CERAD score. Unlike age, years of education showed an independent positive association with all aforementioned cognitive aspects in addition to phonemic fluency (Table 3). Males showed better delayed memory recall but worse

Table 2 The rate of cognitive impairment at baseline and at one year follow-up

	Domains	Subtests	Raw scores	Impairment		
				None	Mild*	Severe**
Baseline	Executive functions	Semantic fluency	**15.27 ± 5.19**	**69.3%**	**15.7%**	**15.0%**
		Phonemic fluency	**7.27 ± 4.14**	**67.2%**	**12.5%**	**20.3%**
	Language	Naming	**13.42 ± 1.67**	**85.0%**	**6.4%**	**8.6%**
	Verbal memory	Immediate memory recall	**16.27 ± 4.34**	**59.1%**	**15.9%**	**25.0%**
		Delayed memory recall	**5.16 ± 2.37**	**76.4%**	**10.0%**	**13.5%**
		Memory recognition	8.46 ± 1.77	70.0%	11.8%	18.1%
	Constructive praxis	Constructive praxis	**9.35 ± 1.53**	**71.1%**	**10.3%**	**18.6%**
1 year-Follow-up	Executive functions	Semantic fluency	**15.26 ± 5.43**	**69.5%**	**17.7%**	**12.8%**
		Phonemic fluency	**7.37 ± 4.06**	**65.8%**	**13.2%**	**21.0%**
	Language	Naming	**13.42 ± 1.72**	**85.2%**	**8.2%**	**6.6%**
	Verbal memory	Immediate memory recall	**16.30 ± 4.74**	**64.2%**	**11.5%**	**24.3%**
		Delayed memory recall	**5.34 ± 2.35**	**76.5%**	**12.3%**	**11.1%**
		Memory recognition	8.45 ± **1.97**	74.1%	10.7%	15.2%
	Constructive praxis	Constructive praxis	**9.34 ± 1.45**	**72.0%**	**11.5%**	**16.5%**

Comparison between the frequency of cognitive impairment in patients at baseline (top row) and after one year of follow-up (bottom row). In analysis of variance (ANOVA) with repeated-measures, no significant difference in z-scores between baseline cognitive profile and those at 1-year follow up in any domain was found, suggesting no significant main effect of *time* ($F(1, 239) = 2.264$; $p = 0.134$)

*-1.99 ≤ z-score ≤ -1.5; ** z-score ≤ -2.0. **Bold print:** considered in the classification

constructive praxis than females ($\beta = 0.821$, $p < 0.001$; $\beta = -0.62$, $p < 0.001$, respectively). Hemoglobin level was independently positively associated with semantic fluency ($\beta = 0.627$, $p < 0.01$), but showed no significant correlation with other cognitive domains (p = NS). Depression showed an independent negative association with delayed memory recall and CERAD score ($\beta = -1.062$, $p < 0.01$; $\beta = -4.3$. $p < 0.05$, respectively). Although hypertension showed a significant correlation with delayed memory recall and naming ability, the association did not remain significant after adjusting for confounding factors (p = NS) (Tables S1 and 3). Interestingly, smoking showed an independent positive association with phonemic fluency ($\beta = 1.146$, $p < 0.01$). History of stroke or TIA did not show a significant association with performance in cognitive tests (p = NS).

Dialysis-specific factors and their association with performance in cognitive tests

Neither dialysis duration (months) nor duration of dialysis session (hours) showed a significant association with performance in the aforementioned cognitive tests (p = NS) (Table S1). Likewise, dialysis efficiency, estimated with equilibrated Kt/v, and calcium-phosphate-product showed no association with performance in cognitive tests. As shown in Table 1, duration of dialysis (months), duration of dialysis session (hours), and equilibrated Kt/v did not differ significantly among the 3 study groups. Calcium-phosphate-product was marginally significantly higher in the group with severe cognitive impairment compared with that with no cognitive impairment ($p = 0.049$) (Figs. 1, 2).

Cognitive profile of hemodialysis patients and its development over one year

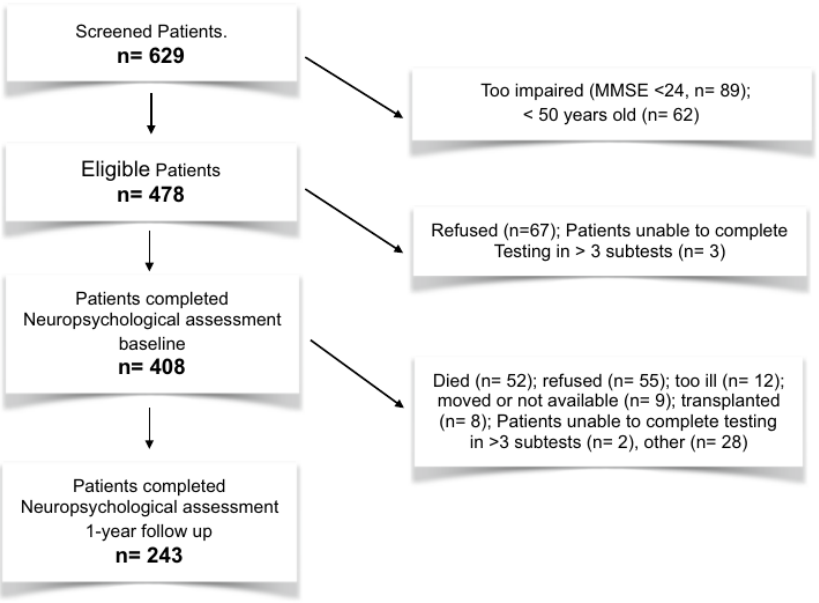
ANOVA with repeated-measures showed no significant difference in z-scores between baseline cognitive profile and those at 1-year follow up, suggesting no significant short-term effect of *time* ($F(1, 239) = 2.264$; $p = 0.134$) However, we found a significant *group-by-time* interaction effect ($F(3, 239) = 3.196$, $p < 0.05$), as shown by a different development of z-scores at one-year follow-up in relation to the grade of cognitive impairment at baseline (differences in z-values between baseline and 1-year follow-up: no cognitive impairment group: – 0.192; mild cognitive impairment = – 0.027; moderate cognitive impairment = – 0.062; severe cognitive impairment = 0.077). The main effect *test* presents significant differences in performance among subtests ($F(4.60, 1099.63) = 24.439$; $p < 0.001$). Bonferroni-corrected pairwise comparisons indicated that patients had the lowest scores in immediate recall (dr), phonemic (pf) and semantic fluency (sf). While no significant effects were found between these three items (dr vs. pf: $p = 1.0$; dr vs. sf: $p = 0.289$; pf vs. sf: $p = 1.0$), all z-scores in the three tests were significantly lower compared to z-scores in the following subtests; delayed recall

Table 3 Multivariate multiple regression analysis showing factors affecting performance in different cognitive tests

	semantic fluency	phonemic fluency	immediate memory recall	delayed memory recall	memory recognition	Naming	constructive praxis	CERAD-Score
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI) /	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Age (years)	– 0.07** (– 0.12– – 0.02)		– 0.148*** (– 0.189– – .107)	– 0.080*** (– 0.102– – 0.057)	– 0.051*** (– 0.068, – 0.035)	0.03*** (– 0.046– – 0.014)	– 0.014 (– 0.029– 0.001)	– 0.395*** (– 0.494– – 0.296)
Years of education	0.541*** (0.327– 0.756)	0.428*** (0.259– 0.597)	0.196* (0.019– 0.373)	0.115* (0.026– 0.014)	0.152*** (0.083– 0.220)	0.142*** (0.076, 0.207)	1.107*** (0.678– 1.535)	0.152*** (0.083– 0.220)
Sex (male vs. female)				0.821*** (0.366– 1.277)			– 0.620*** (– 0.929, – 0.310)	
Hemoglobin (g/dl)	0.627** (0.241– 1.041)							
Depression(vs. no depression)				– 1.062** (– 1.825– – 0.299)		– 0.541 (.– 1.107– 0.025)		– 4.313* (– 7.786, – 0.839)
Arterial hypertension (vs. Normotension)						– 0.403 (– .806, 0)		
Smoking (pack–year)		1.146** (0.316– 1.976)					0.264 (– 0.050– 0.577)	
TIA / Stroke								– 2.902 (– 5.938– 0.135)

β: unstandardized regression coefficient; 95% CI: confidence interval;; *$p < .05$; **$p < .01$; ***$p < .001$

Fig. 1 Flow chart of the study



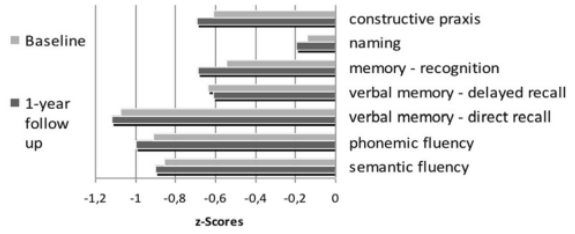


Fig. 2 Cognitive profile of hemodialysis patients. The cognitive profile at baseline and at 1-year-follow up for all patients is shown. In analysis of variance (ANOVA) with repeated-measures, we found no significant difference in z-scores between baseline cognitive profile and those at 1-year follow up in any domain, suggesting no significant main effect of *time* (F(1, 239) = 2.264; $p = 0.134$)

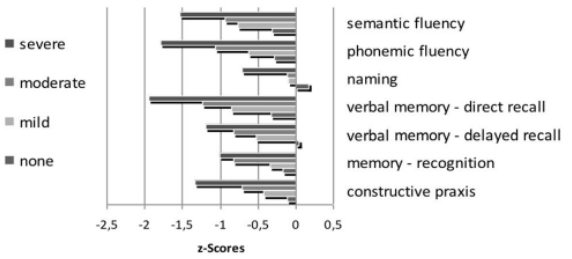


Fig. 3 *Group-by-time* interaction effect (F(3, 239) = 3.196, $p < 0.05$), as shown by a different development of z-scores at one-year follow-up in relation to the grade of cognitive impairment at baseline (differences in z-values between baseline and 1-year follow-up). All domains reveal an impairment in cognitive performance. Bonferroni-corrected pairwise comparisons indicate that patients had the lowest scores in immediate recall (dr), phonemic (pf) and semantic fluency (sf),while no significant effects were found between those three (dr vs. pf: $p = 1.0$; dr vs. sf: $p = .289$; pf vs. sf: $p = 1.0$). All z-scores in the three tests were significantly lower compared to z-scores in the subtests of delayed recall (der; vs. dr: $p < .001$; vs. pf: $p < .01$; vs. sf: $p < .05$), memory recognition (mr; vs dr: $p < .001$; vs. pf: $p < .01$; vs. sf: $p < .05$), naming (na; vs dr: $p < .001$; vs. pf: $p < .001$; vs. sf: $p < .001$) and constructive praxis (cp; vs. dr: $p < .001$; vs. pf: $p < .05$). Only the difference between the semantic fluency and constructive praxis subtests failed significance. der: delayed recall; dr: direct recall, pf: phonemic fluency, sf: semantic fluency, mr: memory recognition, cp: constructive praxis, naming: na

(der; vs. dr: $p < 0.001$; vs. pf: $p < 0.01$; vs. sf: $p < 0.05$), memory recognition (mr; vs dr: $p < 0.001$; vs. pf: $p < 0.01$; vs. sf: $p < 0.05$), naming (na; vs dr: $p < 0.001$; vs. pf: $p < 0.001$; vs. sf: $p < 0.001$), constructive praxis (cp; vs. dr: $p < 0.001$; vs. pf: $p < 0.05$). Only the difference between the semantic fluency and constructive praxis subtests failed significance. The results are illustrated in Fig. 3.

The highest scores were reached in the naming test (vs. der: $p < 0.001$; vs. mr: $p < 0.01$; vs. cp: $p < 0.001$). There was significant interaction between the factor *test* and *cognitive impairment* at baseline, F (13.80, 1099.63) = 1.726, $p < 0.05$, indicating that the profile was mostly shaped through more severely impaired patients. We also found a significant main effect for the amount of cognitive impairment at baseline, F(3, 239) = 71.181, $p < 0.001$. Contrasts were performed comparing each test to z-scores in the immediate memory recall subtest across the different impairment groups. These revealed a significant interaction when comparing the different cognitively impaired groups at baseline. The following interactions were found: Immediate memory recall

compared with tests of (1) delayed memory recall (F[3, 239] = 3.551; $p < 0.05$), (2) memory recognition (F[3, 239] = 4.788; $p < 0.01$), and (3) on naming (F[3, 239] = 3.55; $p < 0.05$), but no interactions were found on (4) semantic fluency (F[3, 239] = 1.523; $p = 0.209$), (5) phonemic fluency (F[3, 239] = 0.299; $p = 0.876$), or (6) constructive practice (F[3, 239] = 0.942; $p = 0.421$). Therefore, the results in the pairwise comparison show that the patients who were already severely cognitively impaired at baseline continued to decline in cognitive performance in the follow-up examination.

To recapitulate the previous results, the amount of decrease in cognitive performance differs depending on the starting level. The cognitive profile showing the worst results in immediate memory recall, phonemic and semantic fluency and the best in naming, is more distinctive in patients that were more severely impaired.

Therefore, we performed further ANOVAs with repeated-measures separately for the different degree of impairment at baseline. As presented in table S2, there was only a significant main effect of *time* in patients who were not impaired at 1-year follow-up (F[1,68] = 13.311, $p < 0.01$), but not in the other groups (mild impairment: F[1, 31] = 0.096, $p = 0.758$; moderate impairment: F[1,83] = 1.341, $p = 0.250$; severe impairment: F[1,57] = 1.100, $p = 0.299$). The known main effect of the factor *tests* was found in all groups (no impairment: F[4.825,328.076] = 6.182, $p < 0.01$; mild impairment: F[4.685, 145.245] = 4.056, $p < 0.01$; moderate impairment: F[3.879, 321.923] = 11.381, $p < 0.001$; severe impairment: F[4.585, 261.368] = 11.538, $p < 0.001$). The interaction between the factors *time* and *test* failed significance in all groups (no impairment: F[5.074, 345.045] = 1.276, $p = 0.273$; mild impairment: F[4.469, 138.544] = 1.788, $p = 0.127$; moderate impairment: F[5.329, 442.267] = 0.479, $p = 0.803$; severe impairment: F[5.159, 294.05] = 0.815, $p = 0.543$).

To explore the differences in the decrease of cognitive impairment in a more detailed manner, we performed paired-sampled *t*-tests separately for the cognitive status at the beginning of this study. We used the CERAD-Score as an independent variable because we had already explored the cognitive profile and there was no sign of different change over time depending on the test. The differences between the CERAD-scores at baseline compared to the scores one year later were only significant in patients with no impairment at baseline ($t[64] = 3.170$, $p < 0.01$, mean difference [md] = 2.74 [SD: 6.94; CI: 1.01, 4.46]), but not in the other groups (mild impairment: $t[30] = -0.984$, $p = 0.333$, md = – 1.06 [SD: 6.02; CI: – 3.27, 1.14]; moderate impairment: $t[82] = 0.806$, $p = 0.423$, md = 0.73 [SD: 8.31; CI: – 1.08, 2.55]; severe impairment: $t[57] = 0.000$, $p = 1.0$, md = 0 [SD: 7.40; CI: – 1.95, 1.95].

Analyses using the last observation carried forward method confirmed the results, except for significant differences in the performance in semantic fluency and constructive praxis, and slight differences in planed contrasts.

Depression was the most influential variable next to age and education in the regression analyses. Therefore, we analyzed whether depression also had an influence on the development in cognitive performance over 1 year, again using the CERAD-Score as an independent variable. We calculated the 2 × 2 ANOVA (time × depression) with repeated-measures for the whole sample because of the small number of depression diagnoses.

There was a significant main effect for *time* (F[1, 235] = 16.539, $p < 0.001$), but even more interestingly, there was also a significant interaction between *time* and *depression*, F(1, 235) = 13.363, $p < 0.001$). This indicates a decrease in cognitive performance for people with depression (Mean = 62.89, SD = 10.27; Mean = 55.94, SD = 11.63), but not for patients without (Mean = 69.20, SD = 10.77; Mean = 68.83, SD = 12.14).

We also found the expected main effect of *depression*, F(1, 235) = 13.061, $p < 0.001$, showing lower CERAD-Scores at baseline and at 1-year follow-up in patients with diagnosed depression compared to those without. Analysis with last observation carried forward did not reveal different results.

Discussion

We used a comprehensive neuropsychological test battery (CERAD) to examine the cognitive profile of cognitive function in hemodialysis patients.

In our study, we described a high frequency of cognitive impairment in hemodialysis patients. At baseline, 75% of the patients suffered from some degree of cognitive impairment, 24% of whom were severe. This is in accordance with previous studies reporting a range from 30 to 80% for cognitive impairment [1, 3, 5, 6, 19].

The most impaired cognitive performance was immediate memory recall, phonemic and semantic fluency, and the best performance was observed in naming. Impaired verbal memory tests involving dialysis patients have been previously reported [8, 20–22]. Other studies found significant differences in cognitive impairment in executive functions, processing speed, word fluency and short-term verbal and non-verbal memory capacity [23, 24]. One study also showed that all patients performed worse in all cognitive domains, especially in memory recall and executive functions [25]. Most of these studies evaluated the decrease in cognitive performance using the MMSE [26], a short neuropsychological screening test that is able to detect progression of cognitive impairment in hemodialysis patients.

As the MMSE may underestimate the extent of cognitive impairment, we used the more comprehensive CERAD battery.

Patients with ESRD displayed a higher prevalence of vascular risk factors, such as hypertension and previous stroke, than the general population without CKD [27]. Vascular disease is a more likely cause of cognitive impairment than Alzheimer's disease in hemodialysis patients [28]. Surprisingly, the study population (with and without cognitive deficit) did not differ significantly with regard to the common vascular risk factors. In the literature it is reported that there is a significant difference in the prevalence of hypertension in patients with cognitive impairment [29], however this was found in a pre-dialysis CKD population. Furthermore, the history of stroke or TIA did not differ significantly in the various groups of our patients with different degrees of cognitive impairment. One reason for this could be that dialysis patients tend to have silent cerebral infarctions [30]. However, as not all patients had MRI imaging available, we could not prove this hypothesis.

Overall, our results suggest that an underlying vascular disease is not the main determinant of cognitive deficits, and also suggest to consider further elements for explaining the cognitive decline in hemodialysis patients.

Moreover, anemia, secondary hyperparathyroidism, dialysis disequilibrium and uremic toxins have also been reported as causes of cognitive impairment in CKD [31], as well as dialysis duration [32]. Dialysis vintage (months) and duration of the dialysis session (hours) showed no association with cognitive performance in our patients. Taking into account that all patients showed good dialysis efficiency, as measured by a Kt/v > 1.2, a negative impact of lower dialysis efficiency on cognitive function cannot be excluded.

We also collected and analyzed some relevant laboratory data. One study showed that dialysis patients with higher hematocrit levels performed better in working memory and attention than patients with lower hematocrit levels [33]. This is in accordance with our results, that showed a positive effect of hemoglobin on the performance in semantic fluency. We also found a positive effect of nicotine on phonemic fluency. There is evidence in literature for an enhancing effect of nicotine on some cognitive functions, like verbal memory and executive functions, nonetheless, nicotine abuse remains harmful in other ways [34].

Lower levels of education are associated with cognitive impairment in our study, as reported by others [32, 35, 36]. This may be explained by the association of lower education levels with poor functional and cognitive reserves.

Interestingly, we have additionally found that the amount of reduction in cognitive performance differed between groups and depended on the initial cognitive level. Decline between CERAD-scores at baseline compared to the scores at one-year follow up was only significant in patients with no impairment at baseline, but not in patients who were already cognitively impaired at baseline. A possible explanation for this could be a floor effect (i.e. not enough variance in already impaired patients).

Depression in hemodialysis patients is very common [37]. To evaluate the frequency of depression and its effect on cognitive performance, the Geriatric depression scale (GDS) was adopted, and in our study depression was found to be significantly associated with cognitive impairment. Other studies have also found similar decline in cognition with the presence of depression [32, 38, 39]. This can be explained by the effects of symptoms of depression on domains of executive functioning and processing speed, in keeping with previous studies [39].

Of note, depression is often under-diagnosed in patients with CKD [40]. Only 3.9% of the unimpaired patients suffered from depression, whereas 9.8% (mild cognitive impairment) and 10% (severe cognitive impairment) of our patients fulfilled the criteria for depression. Estimates for the prevalence of depression in patients with CKD and ESRD range widely from 20 to 40% [37, 40]. In contrast, only a low percentage of our patients were considered as suffering from depression. A possible explanation could be the different methods for the diagnosis of depression in the studies. In our study, we used the GDS, which is a short and inexpensive instrument for measuring depressive symptoms in older adults. However, the GDS can only be used as a screening instrument. The application of more comprehensive depression scales like the Beck Depression Inventory or the Montgomery Asberg Depression rating scale may lead to different conclusions.

Some studies reported a time testing effect with optimal function 24 h after dialysis and worsening with time since the last dialysis session [21, 41–44]. The first studies were conducted when acetate dialysate was still in use. A recent study was able to rule out a significant time-dependent effect, without differences when the patients were tested during or after dialysis [45].

Cognitive performance in hemodialysis patients depends also on the testing environment, and the performance was better when tests were carried out in a separate room [46]. In our study we used the real dialysis setting (a room with two or three other patients).

Our study carries some limitations. The test environment may not have been optimal, but having a quiet place for each patient during the testing was not possible. On the other hand, test conditions reflected the usual dialysis setting. Discussions with patients, changes in medication and important decisions are made during dialysis.

Monitoring the change in cognitive performance after 1 year of dialysis is frequently employed (Ref. [47]), however, it would be interesting to test the changes over a longer period of time. Finally, it has to be mentioned that

the CERAD test battery is widely used to detect cognitive impairment, but has not been specifically validated in dialysis patients.

In conclusion, creating a neurocognitive profile in hemodialysis patients is important as the prevalence of cognitive impairment, which is related to educational level, is high and is affected by depression. As depression has a significant influence on cognitive impairment, its early identification may allow to timely initiate treatment and positively influence cognitive performance. The neurocognitive profile and the definition of the deficits may allow to establish individual training programs to control and reduce cognitive deficits.

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Authors' contributions HK designed the study, collected data analyzed and interpreted the clinical data and wrote the manuscript; KB analyzed and interpreted the data; JZ analyzed the data; RD analyzed and interpreted the data critically and revised the manuscript; JH designed the study, collected analyzed data, interpreted the clinical data and critically revised the manuscript. All authors approved the final version of the manuscript.

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Declarations

Conflict of interest Each author certifies that he or she, or a member of their immediate family, has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the contents of the submitted article. The results presented in this article have not been published previously in whole or part, except in abstract format.

Availability of data and material The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability No new code was produced in this study.

Ethics approval and consent to participate This study was approved by the ethics committee of the University of Marburg and conforms to the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to study enrollment.

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4.2. COGNITIVE PERFORMANCE IN DIALYSIS PATIENTS – „WHEN IS THE RIGHT TIME TO TEST?" (A2)

***Hristos Karakizlis**, Stefanie Thiele, Brandon Greene, Joachim Hoyer*

Kognitive Beeinträchtigungen bei chronischen Nierenerkrankungen, insbesondere bei terminaler Niereninsuffizienz, sind ein gesundheitsökonomisches Problem. Dennoch sind die Ursachen nach wie vor unklar. Die Prävalenz von kognitiven Beeinträchtigungen bei Patienten mit terminaler Niereninsuffizienz liegt bei bis zu 87 %.

Die vorliegende Studie befasste sich mit der Erforschung der – möglichen – Auswirkung des Untersuchungszeitpunktes auf die kognitive Leistungsfähigkeit bei Hämodialysepatienten. Wir testeten die kognitive Leistungsfähigkeit mit einer neuropsychologischen Testbatterie (RBANS, Repeatable Battery for the Assessment of Neuropsychological Status) an 2 verschiedenen Zeitpunkten während der Dialyse sowie an einem dialysefreien Tag. Darüber hinaus wurden bei allen Teilnehmern der GDS (Geriatric Depression Scale) untersucht und verschiedene demografische und klinische Variablen erfasst, um ihren möglichen Einfluss auf die kognitive Leistungsfähigkeit zu untersuchen.

Die Patienten wurden in 3 Dialysezentren in der Region Mittelhessen, Deutschland, rekrutiert. Die 26 Teilnehmer absolvierten 3 Testungen über einen Zeitraum von 6 Wochen in den Dialysezentren.

Die Patienten erzielten in den ersten 2 Stunden nach der Dialyse mit 81,1 Punkten die beste kognitive Leistung im RBANS. Beim Vergleich der Werte der 3 Messzeitpunkte (erste 2 Stunden, Zeitpunkt 1 vs. letzte 2 Stunden, Zeitpunkt 2 vs. dialysefreier Tag, Zeitpunkt 3) wurde jedoch kein signifikanter Unterschied festgestellt. Allerdings zeigten die Patienten sowohl in den ersten 2 Stunden ($p < 0{,}001$) als auch in den letzten 2 Stunden der Dialysebehandlung ($p < 0{,}001$) eine signifikant bessere kognitive Leistung in der Sprache im Vergleich zum dialysefreien Tag.

Aufgrund der hohen Prävalenz kognitiver Beeinträchtigungen wird es immer wichtiger, die kognitive Funktion bei Dialysepatienten richtig zu beurteilen. Unsere Daten zeigen, dass der Zeitpunkt der Untersuchung (erste 2 Stunden an der Hämodialyse vs. letzte 2 Stunden an der Hämodialyse vs. dialysefreier Tag) keinen Einfluss auf die kognitive Gesamtfunktion bei Hämodialysepatienten in Routine-Indikationen hatte.

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Cognitive performance in dialysis patients - "when is the right time to test?"

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Abstract

Background: Cognitive impairment in chronic kidney disease, especially in end stage renal disease, is a public health problem. Nevertheless, the cause of chronic kidney disease still remains unclear. A prevalence of cognitive impairment in patients with end stage renal disease of up to 87% has been found.

Methods: The study at hand deals with the research on the – potential – effect of timing on cognitive performance when testing cognitive impairment in hemodialysis patients during the dialysis cycle. We tested cognitive performance with a neuropsychological test battery (RBANS, Repeatable Battery for the Assessment of Neuropsychological Status) on two occasions while patients were on dialysis as well as on a dialysis-free day. In addition, all participants were rated using the Geriatric Depression Scale (GDS) and several demographic and clinical variables were recorded in order to investigate their possible influence on cognitive performance.
The patients were recruited in three dialysis centers in the central region of Hesse, Germany. Twenty-six participants completed the 3 testings during a period of 6 weeks. The testing was carried out in the dialysis centers.

Results: Looking at the total scale score, patients achieved the best cognitive performance in the RBANS during the first 2 h on dialysis with 81.1 points. When comparing the scores of the three measurement occasions (first 2 h, Timepoint 1 vs. last 2 h, Timepoint 2 vs. dialysis free day, Timepoint 3, however, no significant difference in the total scale score was detected. But patients showed significantly better cognitive performance in language in the first 2 h ($p < 0.001$) as well as in the last 2 h ($p < 0.001$) compared with the dialysis-free day.

Conclusion: Due to the high prevalence of cognitive impairment, there is an increasing need to assess cognitive function in dialysis patients. Our data show that the time point of testing (first 2 h on hemodialysis vs. last 2 h on hemodialysis vs. Hemodialysis free day) had no influence of cognitive function in hemodialysis patients in routine indications.

Keywords: RBANS, Cognitive performance, Hemodialysis patients, Neurocognitive testing, Cognitive impairment

Background

Cognitive impairment in chronic kidney disease (CKD), especially in end-stage-renal-disease (ESRD), has increasingly been researched on in the last years but the cause of CKD is still unknown and might be multifactorial. As the prevalence of cognitive impairment especially in patients with ESRD is up to 51–76% [1, 2], partly up to 87% [3] it is necessary and important to focus on both cause and diagnostic. Especially because hemodialysis patients need cognitive skills to understand and follow health-related information [4].

Several factors such as older age [5] and worsening kidney function itself [6–9] can cause cognitive impairment as well as uremia [10, 11] and cerebrovascular diseases [12]. We would like to emphasize that patients with CKD and especially ESRD have a higher risk of incident stroke [13–15] and have a higher prevalence of white matter lesions and silent brain infarcts [16, 17]. Further, white matter hyperintensity and ventricular and hippocampal atrophy is associated with

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cognitive impairment [18] and patients with a history of stroke or silent brain infarcts have an increased risk of dementia [16, 17, 19]. Also, the presence of depression can affect the results of cognitive performance [9, 20].. There are several test procedures for detecting depression, of which the Geriatric Depression Scale (GDS) is a test frequently used in clinical practice.

Low diastolic blood pressure in the elderly appears to be associated with an increased risk of developing dementia [21]. Intradialytic hypotension is a common phenomenon of hemodialysis patients and occurs in over 30% of patients and is not only associated with increased mortality [22] but also appears to have an impact on the cognitive performance of dialysis patients. The relationship between cognitive impairment and the reduction of cerebral blood flow has also been shown in recent retrospective and prospective studies [23, 24].

As hemodialysis patients are subject to acute hemodynamic changes and large fluid shifts during dialysis previous studies investigated that the point of testing cognitive impairment is relevant. Especially the dialysis itself causes acute deterioration to the patients compliance and could lead to not understanding medication plans when the doctor patient communication takes place during dialysis [25].

Since hemodialysis itself seems to affect cognitive function several studies investigated whether the time point of testing might lead to different results in cognitive functioning. Thus one previous study suggested that cognitive function was worse during dialysis and best the day after dialysis [25]. In addition to these findings further studies found that cognitive function seems to be best the day after dialysis in comparison shortly before dialysis [26, 27]. When focusing on the time directly after dialysis, however, the results differed from the findings of the other studies. While one study result shows an improvement in global neuropsychological functioning [28] other studies demonstrate that cognitive function gets worse after dialysis and the greatest cognitive impairment seems to be 67 h after dialysis [10]. In accordance with these findings individual cognitive fluctuations with mainly a decline in attention and executive function after dialysis were described [29]. Studies with a greater interval between their testing showed no difference in cognitive functioning [30].

Due to these various findings, we investigated whether the point of testing hemodialysis patients during a dialysis cycle in comparison to the day after dialysis has an effect on cognitive performance.

Methods

General data

We studied cognitive performance with a neuropsychological test battery (RBANS, Repeatable Battery for the Assessment of Neuropsychological Status) while patients were on dialysis as well as on a dialysis-free day. For better comparability the neuropsychological battery was administered three times: firstly, during the first 2 hours of dialysis (T1), secondly during the second 2 h of dialysis (T2) and thirdly on a dialysis-free day (T3). All three tests were carried out within a time interval of two weeks, respectively. The GDS was also performed once on all participants to assess the possible influence of depression.

The tests were conducted with a "standard dialysis population" in the administrative region of "Middle Hesse" at three separate outpatient dialysis centers. Criteria to be included in the study were: at least 18 years of age, native German speaker and at least 6 months on dialysis. Patients under the legal supervision of a guardian were excluded from the study. Recruitment was carried on until the desired number of 31 participants was reached.

This study was approved by the ethics committee of the University of Marburg and conforms to the Declaration of Helsinki. Written informed consent was obtained from of all participants.

RBANS

The RBANS is a brief, individually-administered test measuring cognitive function across five domains: attention, language, visuospatial/constructional abilities, and immediate and delayed memory. Performance in each domain is measured by the subtests (12 in total) described below, which are combined to yield five scaled "index scores" gauging function in the respective domains. These five index scores are in turn combined to yield a composite score referred to as the "total scale score". Stimuli are contained in a wire-bound, easel-type booklet, making the test easily portable and allowing for bedside administration. Total administration time is 20–30 min. Normative information from the manual for the index and total scores is based on 540 healthy adults who ranged in age from 20 to 89 years [31, 32].

The battery was designed to be amenable to the construction of multiple equivalent forms, and there are different, equivalent versions of the RBANS available for test-retest use.

The domains comprise the following subtests:

1. Immediate Memory

a) List Learning: immediate recall of a 10-item list of words.
b) Story Memory: a 12 item story, read aloud for immediate recall over two trials [32].

2. Visuospatial/Constructional

a) Figure Copy: copying a geometric figure of 10 parts.

b) Line Orientation: a 10 item line orientation test [32].

3. Language

a) Picture Naming: 10-line drawings which the subject must name
b) Semantic Fluency: the total number of examples generated for a given semantic category within 60 s [32].

4. Attention

a) Digit Span: analogous to digits forward on the WAIS [33]. There are two strings of digits in each item, each pair increasing in length from 2 to 9 digits. The second string of a given length is only read if the first string is failed.
b) Coding: numbers rather than symbols were chosen for the response in order to avoid the possible detrimental effect of a constructional apraxia on performance [32].

5. Delayed Memory

a) List Recall: free recall of the words from the List Learning task.
b) List Recognition: yes/no recognition testing for memory of the words from the List Learning task.
c) Story Recall: free recall of the story from the story memory test.
d) Figure Recall: free recall of the figure from the figure copy subtest [32].

All subtests of the RBANS were scored according to standardized age-adjusted criteria. Raw scores from the 12 subtests were converted to age- adjusted scaled scores before calculating an index score for each domain. The sum of the index scores was then converted to a total scale score.

Tests and testing order

For each patient all three tests, including tests on the dialysis-free day, were conducted on site in the dialysis center. All testing was carried out by the same person who was trained prior to the commencement of the neuropsychological assessments.

Before testing we randomized the order of testing (T1, T2 and T3) for each patient to avoid possible confounding effects of the test scores due to learning effects. Thus, for each patient it was randomly chosen at which time point in the dialysis cycle the RBANS was administered to the individual for the first, second and third time. For every desired test time a different version of the RBANS was used: version A at T1, version B at T2 and version C at T3.

Additional data

In addition to the RBANS, all participants were rated using the Geriatric Depression Scale and several demographic and clinical variables were recorded in order to investigate their possible influence on cognitive performance, such as age, sex, education, dialysis rhythm and duration, type of dialysis, years of dialysis, and possible nicotine, alcohol or drug abuse leading to renal disease. Independent mortality risk factors such as coronary heart disease, myocardial infarction, arterial hypertension, diabetes mellitus, stroke, dementia, depression as well as vital signs such as blood pressure and heart rate, and laboratory values, such as hemoglobin, albumin, pH, bicarbonate, cholesterol, creatinine, urea and Quality of Dialysis measured in Kt/V were also considered.

Statistical analysis

For statistical computing we used “R program for statistical computing” [34]. We first looked at the measure of central tendency (mean, median, minimal and maximal value) and measure of variation (standard deviation) of the index and total scale score. For further analyses a linear mixed model was used for comparing the five cognitive domains across T1, T2 and T3. The domains are reflected in index scores which are summed in the total scale score. The within-patient correlation in the test scores has been taken into account. A similar mixed model was used to analyze if an increasing trend in patients’ scores with each additional repetition of the test has occurred.

Results

Sample characteristics and patients

Recruitment was carried out in three dialysis centers in the central Hessen region. Twenty-six patients completed all three testings at the predefined test points over a period of 6 weeks. Five patients had to be excluded, due to intercurrent diseases and in-hospital treatments.

The average age of the patients was 64.8 ± 14.4 years. Of these, 19 (73.1%) were male and 7 (26.9%) were female. All patients completed general school education for 9 years, 27% or 15% had school education for one- or three more-years equivalent to advanced high school education. 77% completed vocational training including community college and 15.4% completed academic education at a university. Characteristics and demographic data of the 26 patients are listed in Table 1.

Table 1 Demographics of the patients and etiology of renal diseases

Demographics	Patients (*n* = 26) M (SD)
Age	64.8 (14.4)
Gender	Male 73.1%
School-Education	High-school 57.5%
	Senior-high 26.9%
	College 15.4%
Job-Education	Community college 76.9%
	University 15.4%
	None 7.7%
dialysis vintage (y)	5.65(4.39)
Kt/V	1.7 (0.3)
Blood	
Hemoglobin	11.5 g/dl (1.1)
Creatinine	9.46 mg/dl (2.6)
Albumin	38.2 mg/dl (4.9)
$HCO3^{-}$	23.2 mmol/l (3.3)
Clinical Data	
Blood Pressure	127.8/68.1 mmHg (17.2/11)
Heart frequency	73/min (10.8)
Etiology of renal disease	
Diabetic Nephropathy	23.1%
Vascular/Hypertensive kidney disease	19.2%
Glomerulonephritis and systemic diseases	34.6%
Polycystic kidney disease	3.9%
Unclear	7.7%
Others	11.5%

Kt/V measurement of dialysis quality, *HCO3-* bicarbonate, *y* year

For additional information considering the underlying diseases leading to CKD, laboratory values were recorded. The mean values of our sample showed Hb 11.5 ± 1.1 g/dl, Creatinine 9.46 ± 2.6 mg/dl, albumin 38.2 ± 4.9 mg/dl, HCO3–23.2 ± 3.3 mmol/l, systolic and diastolic blood pressure of 127.8 ± 17.2 mmHg and 68.1 ± 11.0 mmHg respectively, pulse frequency 73 ± 10.8 /min and Kt/V 1.7 ± 0.3.

Cognitive test results

First of all, we looked at the total scale score and the index scores of each individual domain compared across T1, T2 and T3 which are shown in Fig. 1. Comparing the three time points in time of testing (T1 vs. T2, T2 vs. T3 and T2 vs. T3) there was no statistically difference in the total scale score. The best cognitive performance was achieved by using the RBANS at T1 with 81.1 points. At T2 an average value of 79.6 and at T3 of 78.6 points was reached.

Also, by looking at the individual domains' patients showed no significant difference in the scores at T1, T2 and T3 in domain immediate memory, visuospatial/constructional, attention and delayed memory.

Significantly different results were detected in domain 3 (language). Patients showed significantly better cognitive performance in language at both T1 ($p < 0.001$) and T2 ($p < 0.001$) compared with T3. In this domain, test results dropped from 76.5% at T3 to 89.1% at T1 and 90.8% at T2. These results clearly show that the reduction of the scores in domain 3 (language) concerns the entire patient group rather than being an effect of an individual deterioration from one of the patients results (see Fig. 1).

Domain 3 (language) comprising the picture-naming and semantic fluency subtests were further analyzed separately in order to investigate possible reasons for the significant differences in the scores. Therefore, raw scores were analyzed which showed that the deterioration at T3 was present in both of the subtests (see Fig. 2). In the picture naming subtest, the mean dropped from 9.8 at T1 and 9.6 at T2 respectively to 8.7 at T3 (all $p < 0.001$) and in the semantic fluency subtest from 14.7 at T1 and 15.8 at T2 to 10.7 at T3 (all $p = < 0.001$).

As seen before by looking at the index score there is again a reduction in all scores across the whole patient group and not a single poor test result by one of the patients at that time.

Test repetition and learning effects

We also analyzed the index scores and total scale score grouped by looking at the number of test repetitions i.e., if the participant was being administered the test for the first, second or third time. None of the index scores or the total scale score ($p = 0.48$) showed a noticeable trend. Thus, no significant learning effect was detected (see Fig. 3). Noteworthy is the significantly decreasing trend of average 3.8 points per repetition ($p = 0.004$) in domain 5 (delayed memory).

Discussion

The aim of the current study was to evaluate the variability of cognitive performance in relation to the time of testing. The main question was if there is an optimal time of testing dialysis patients. This time should be used as a basis for future research in the field of cognitive impairment in dialysis patients. Neurocognitive testing was set in the first 2 h of dialysis, the last 2 h of dialysis and on dialysis free days. The results of our study indicate that the time point of testing cognitive function by using the RBANS in hemodialysis patients did not show any clinical impact.

No statistically measurable differences in cognitive performance in the overall results (total scale score)

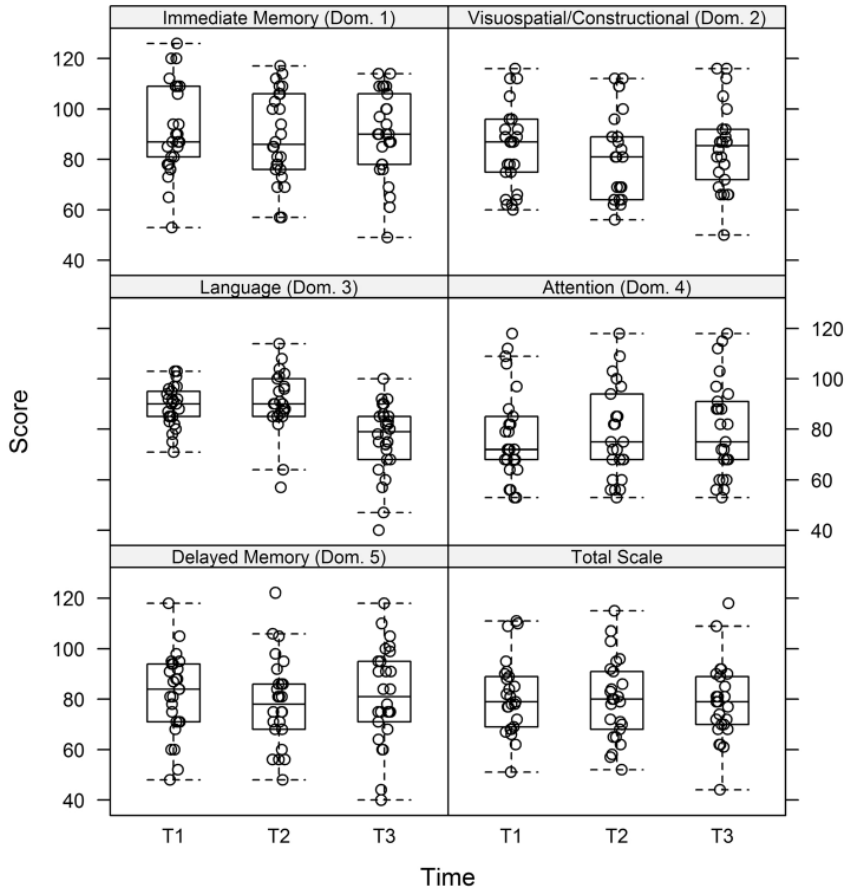

Fig. 1 Index scores of each domain (Dom.) (1–5) and Total Score divided up to the time points. In the total scale there are no differences seen in the index scores. Also, in domain1,2,4 and 5 are no differences in cognitive performance in the individual test times occurred. Domain 3 (language) however, shows a significant difference from the time of testing T1 vs. T2 ($p < 0.001$) and test time of T1 vs. T3 ($p < 0.001$). T1 = timepoint 1, first 2 h on dialysis, T2 = timepoint 2, last 2 h on dialysis, T3 = timepoint 3, dialysis free day

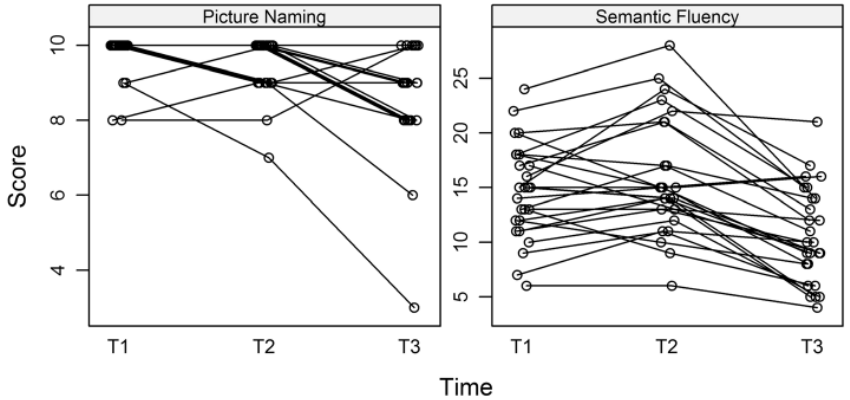

Fig. 2 This figure shows the row-data of the two tests of domain 3 (language). There is a reduction in scores across the whole patients' groups in both tests (Picture Naming and Semantic Fluency) at test-time-points. T1, T2 and T2. T1 = timepoint 1, first 2 h on dialysis, T2 = timepoint 2, last 2 h on dialysis, T3 = timepoint 3, dialysis free day

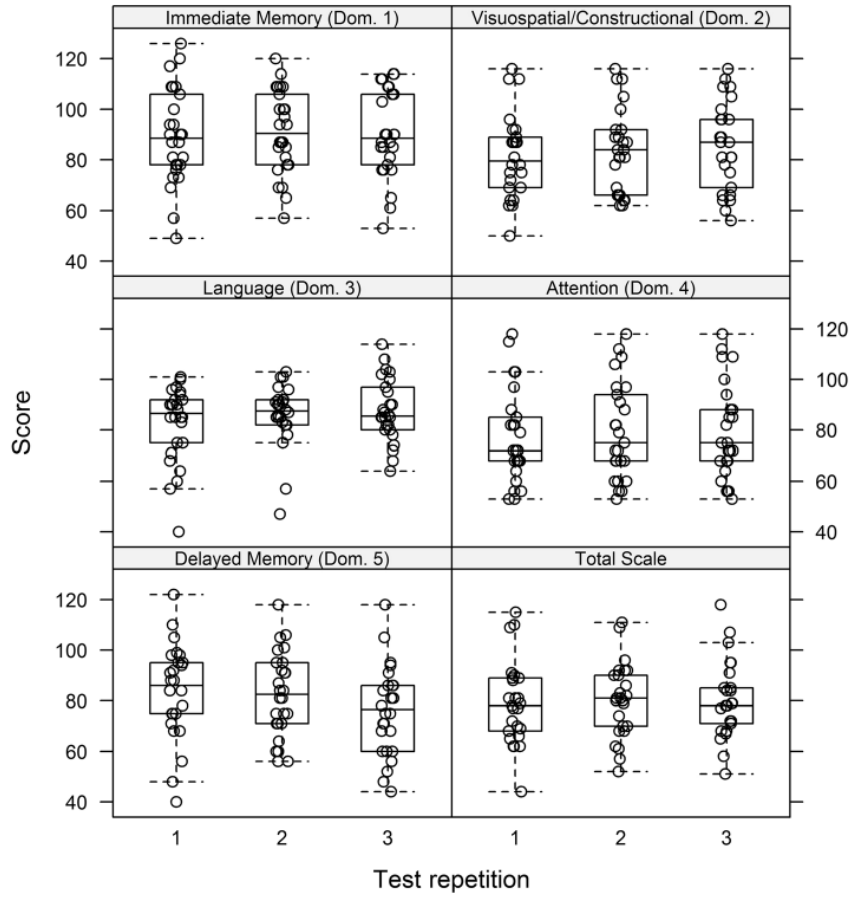

Fig. 3 Index Scores of the domains (Dom.) 1 to 5 and Total scale score by number of test repetitions. No learning effect was seen during the various test-time points

were detected. By looking at the individual domains poorer cognitive performance was seen in domain 3 (language) on the dialysis-free day (T3) in comparison to the two remaining points in time of testing during dialysis (T1 and T2).

In contrast to our results previous studies reported that the "optimal" time point for carrying out the test is 24 h after dialysis [10, 25]. However, dialysis treatments of the past that date back to the times of acetate dialysis [10] cannot be compared with nowadays modern treatments of dialysis with bicarbonate. Nausea and vomiting were extremely common among patients using these older methods, which could be a possible explanation why they achieved better test results on the dialysis-free days.

A study from 2007 using 30 dialysis patients demonstrated that the best cognitive performance was achieved on a dialysis-free day and that the first hours of dialysis were associated with significantly worse cognitive performance [25]. Here, a comprehensive test battery with an analysis of different cognitive domains was used, and especially in the domains "delayed verbal and visual immediate memory" a significantly impaired cognitive performance was seen during testing on dialysis. While language was not affected, a moderate difference in cognitive performance was found in the field of executive function [25]. A possible reason for the differing results in our study is that all patients were tested at the predefined test points over a period of 6 weeks, whereas in the study by Murray et al. the number of patients who did not complete all tests was greater (15 of 33 patients were not tested at all test sessions).

The use of different study designs could be another explanation for the differing results. In order to avoid possible learning effects, we left a time period of 14 days between every testing, selected a test battery for repeated measurements to be used at T1, T2 and T3 and randomized the sequence of test sessions T1, T2 and T3 for each patient.

In another study of Drew et al., cognitive performance was tested on a total of 40 patients just before dialysis

and during the first hour after the beginning of the dialysis session. Their findings are consistent with our results, as there were no significant differences in cognitive performance between the time points of investigation [30]. However, in that study, a test on the dialysis-free day was not performed.

Williams et al. in 2004 reported a decline in cognitive performance in hemodialysis patients in auditory memory and in attention with the greatest impairment occurring 67 h after dialysis. However, they did not perform their testing during dialysis, but 1, 24 and 67 h after dialysis [10]. In our study, we did not see any overall deterioration in cognitive performance at the different points of testing, surprisingly we did see a deterioration in cognitive performance in the domain of language at test point T3. In the study of Williams et al., only two subtests showed a change in cognitive performance. The reason for this does not appear to be entirely clear right now. Since the deteriorations occur on dialysis-free days we do not believe that hemodynamic fluctuations are responsible for this. The accumulation of toxins on the non-dialysis day would rather be responsible for the cognitive changes. However, further studies are needed to finally answer this question.

In a cross-sectional observation study of 47 hemodialysis patients in 2014, the majority of patients examined did not show significant individual cognitive variation. The minority of patients who showed a fluctuation in cognitive performance showed a deterioration in attention and executive function after dialysis [29]. This is in accordance to our findings.

In accordance with these findings an improvement of cognitive impairment has also been found after dialysis in global neuropsychological functioning by using a computer based assessment battery [28]. We did not focus on the time after dialysis but the results, and that the majority of patients being tested after dialysis had a stable performance actually confirms the findings of our study.

One recent study also tested the cognitive performance in hemodialysis patients on dialysis and the day after dialysis. The authors hypothesized that a single dialysis improves cognitive function in hemodialysis patients. They showed an improved performance in logical and visual long-term memories after the dialysis session [27]. But, as in our study, neither the performance in short-term and working memories nor in verbal fluency and planning behavior was changed. An almost similar study design with testing before dialysis and the day after with an improvement of cognitive function after hemodialysis especially in attention was described by Griva et al. [26]. The different findings might be explained with the difference in age of the patients. Age is a risk factor for cognitive decline and in both studies patients were approximately 10 years younger than in our sample [26, 27]. Dasgupta et al. report that cognitive function is significantly reduced during hemodialysis treatment in the majority of patients [2]. The main difference between the study design and our study is that the timing of the test was significantly different from ours. We tested during the first 2 h and the last 2 h of dialysis and on the dialysis-free day at 14-day intervals, whereas Dasgupta et al. tested immediately before dialysis and at the end of dialysis and 1 week later shortly before dialysis. Testing on the dialysis-free days did not take place. The differences in the results between the studies appears to be related to the timing of the post-dialysis testing.

A recent study showed a clear relationship between cerebral blood flow and cognitive performance. Patients in the study were tested on dialysis and also on dialysis-free days and showed a significant deterioration in executive function during dialysis treatment [24]. The significant differences between those results and our study results could be explained by the number of hypertensive patients. In our study population there were fewer hypertensive patients which could be less sensitive to blood pressure fluctuations.

One study reported that cognitive performance in hemodialysis patients not only depends in the time of testing but also on the testing environment. As the best cognitive performance was achieved by testing before hemodialysis in a separate room the authors suggest that a standardization test should be used before hemodialysis in a separate room [35]. Bearing in mind that previous studies tested patients in their dialyzing room might partly explain the decline in cognitive performance on dialysis. We are currently unable to confirm this hypothesis as patients in our study were also tested during dialysis in their dialysis room and had no decline in cognitive impairment on dialysis compared to the dialysis free day.

Independent of the time of testing, the study participants showed a high prevalence of cognitive impairment. In accordance with previous findings our results show a decline in cognitive performance in executive functions, language, attention and delayed memory as well as immediate memory [25, 36–38]. It should be mentioned that adhering to the strict scoring criteria of the figure copy and figure recall test might lead to lower raw scores in the visuospatial/constructional and delayed memory subtest [39]. We strictly observed these scoring criteria as the purpose of this study was to compare the results of the different time points without classifying the severity of cognitive impairment.

A potential cause for the high prevalence of cognitive impairment in hemodialysis patients might be a high prevalence of stroke, white matter lesions and silent brain infarcts [17, 24]. As previously determined, there is a high prevalence of cerebral atrophy in hemodialysis patients [17, 40]. Recent studies complement the findings by describing a significant correlation between age and whole brain atrophy as well as hippocampal atrophy and hyperhomocysteinemia [41].

In a further study Harciarek et al. investigated the semantic and phonemic fluency performance in hemodialysis patients and determined a decline in phonetic fluency while patients showed a stable performance in semantic fluency [42]. The stable performance in semantic fluency was also seen in other studies [27, 30] but cannot be confirmed in our study. A possible explanation might be that the missing improvement in semantic fluency seen in the results of Schneider et al. [27] reflect the cognitive decline seen in our result on the dialysis free day.

A consideration of Drew at el. especially on executive function and memory over years in hemodialysis patients showed a decline in executive but not memory function. Age was a strong risk factor for cognitive decline for the executive function [43].

The missing deterioration in memory function, in contrast to our study, might be caused by learning effects. By testing a validated test battery for repeated testing with different test versions we can exclude learning effects and this could be an explanation for the different results.

The current study may be limited by:

- our small sample size and
- patients, who already noticed cognitive impairment themselves, might have rejected from participating in our study.
- the study population of 65 years is slightly younger than the average dialysis patient, which could also have an effect on cognitive performance.
- an overrepresentation of male subjects in our study.

Due to the sample size and the slightly younger age of the study population as well as and the overrepresentation of male subject, the results may not be transferable to the general dialysis collective. Additionally, it must be noted that the tests were conducted in German and therefore the results may not be generalizable to all demographic groups. It is also possible that there were still residual confounders, since possible influencing factors may not yet be known and could not be taken into account.

Nevertheless, the study also has its strengths and advantages:

- First of all, it is a prospective randomized study. In order to exclude learning effects in the individual test points, three different versions of the tests were conducted in each case.
- The second important strength is the implementation of an extensive neurocognitive test battery, which is more sensitive than screening tests in detecting mild cognitive impairment. The cognitive battery used in this study (RBANS) incorporates multiple previously validated cognitive tests and includes different versions. These versions are validated for showing an absence of learning effects when retesting [32]. Therefore, learning effects can be excluded.
- Third, almost all patients included in our study completed the tests on all three predefined testing points.
- Additionally, patients who participated in the study form an average of dialysis patient in terms of education, medical history, gender and underlying disease.

Conclusion

Our study shows that the time point of testing (first 2 h on hemodialysis vs. last 2 h on hemodialysis vs. Hemodialysis free day) had no influence on cognitive function in hemodialysis patients in routine indications. Cognitive tests can thus be used as an element in routine checkup on dialysis patients during the visit. This provides us with an overview of the cognitive function of the patients and can also be used as a course parameter to detect a possible deterioration of the cognitive function at an early stage.

Abbreviations

CKD: Chronic kidney disease; Dom: Domain; ESRD: end stage renal disease; GDS: Geriatric Depression Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; Hb: Hemoglobin; HCO3-: bicarbonate; Kt/V: measurement of Dialysis Quality; T1: Timepoint 1, first 2 h on dialysis; T2: Timipoint 2, last 2 h on dialysis; T3: Timepoint 3, dialysis free day; WAIS: Wechsler adult intelligence scale

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Authors' contributions

Co-authors have all contributed to this manuscript and approve its submission. This manuscript is co-authored by HK (conception and design, collecting data, analysis and interpretation of data, and writing of manuscript), ST (collecting data, interpretation of data, writing of manuscript and critical appraisal of article), BG (analysis), and JH (conception and design, analysis and interpretation of data and writing of manuscript). The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the University of Marburg and conforms to the Declaration of Helsinki. Written informed consent was obtained from of all the participants prior to study enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Publisher's Note

4.3. NEUROPSYCHOLOGICAL ASSESSMENT OF COGNITIVE IMPAIRMENT IN KIDNEY TRANSPLANTATION (NASKIT) AND ITS RELATED RISK FACTORS: A STUDY PROTOCOL (A3)

***Hristos Karakizlis**, Johanna Doerr, Anna Becker, Christian Nahrgang, Lucy Rainer, Ingolf Askevold, Juliane Liese, Winfried Padberg, Mostafa Aly, Rolf Weimer, Martin Juenemann*

In den letzten 10 Jahren wurde von einem Zusammenhang zwischen kognitiven Beeinträchtigungen und chronischer Niereninsuffizienz berichtet. Die kognitive Leistungsfähigkeit ist bei Patienten nach Nierentransplantationen zwar besser als bei Dialysepatienten, aber schlechter als bei der altersgleichen Normalpopulation. Eine bessere Kenntnis der Prävalenz sowie des Verlaufs und des Profils kognitiver Beeinträchtigungen ist für die Konzeption künftiger Studien zur Bewertung der klinischen Auswirkungen kognitiver Beeinträchtigungen und zur Entwicklung von Behandlungsstrategien wichtig. Ziel unserer geplanten Studie ist es, das Ausmaß der kognitiven Beeinträchtigung vor und nach einer Transplantation zu untersuchen und mit Hilfe von neurokognitiven Standardtests ein eindeutiges Profil der kognitiven Funktion zu erstellen. Darüber hinaus wollen wir beurteilen, ob die Transplantation an sich zu einer Verbesserung der kognitiven Leistung führt.

Wir führen eine prospektive monozentrische Kohortenstudie mit 100 nierentransplantierten Personen durch, in die Personen aufgenommen werden, die eine Nierentransplantation erhalten oder bereits erhalten haben. Die Patienten werden zu Beginn der Studie sowie nach 3 und 12 Monaten einer detaillierten neurokognitiven Testbatterie unterzogen. Darüber hinaus werden die Patienten eine validierte deutsche Version des Fragebogens zur kognitiven Beeinträchtigung zur Selbstbeurteilung (s-CFQ) sowie den HADS-D ausfüllen, ein Screening-Instrument mit 2 Skalen zur Erfassung von Angst und Depression. Außerdem wird zu jedem Messzeitpunkt eine Haarprobe entnommen, um das Haar-Cortisol als Parameter für die kumulative Aktivität der Hypothalamus-Hypophysen-Nebennierenrinden-Achse über die letzten drei Monate zu bestimmen. Die primäre Zielgröße ist a) die Auswirkung der Nierentransplantation auf die kognitive Leistung bis zu 12 Monate nach der Transplantation und b) der Verlauf der kognitiven Leistung nach der Nierentransplantation im Zeitverlauf.

Die Ergebnisse unserer Studie könnten unter Umständen wichtige Auswirkungen auf die Prävention und Behandlung kognitiver Beeinträchtigungen bei

nierentransplantierten Personen haben. Das neu gewonnene Wissen über das neurokognitive Profil und die Zuordnung der entsprechenden Defizite könnte dabei helfen, ein individualisiertes Trainingsprogramm zu erstellen, um die kognitiven Defizite bei diesen Personen positiv zu beeinflussen.

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TECHNICAL NOTE

Neuropsychological Assessment of Cognitive Impairment in Kidney Transplantation (NAsKiT) and its related risk factors: a study protocol

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Abstract

Background Association of cognitive impairment with chronic kidney disease has been reported over the last decade. Individuals show better cognitive performance after kidney transplantation than individuals on dialysis but are more likely to be affected by cognitive impairment than age-matched comparison groups. Better knowledge of the prevalence as well as course and profile of cognitive impairment is important for the design of future studies assessing the clinical impact of cognitive impairment and developing management strategies. The goal of our study is to examine the extent of cognitive impairment before and after transplantation and to derive a distinct profile of cognitive function using standard neurocognitive tests. Furthermore, we aim to assess whether transplantation per se leads to an improvement in cognitive performance.

Methods We are conducting a prospective single-center cohort study involving 100 kidney transplant individuals. Individuals who are wait-listed to receive a kidney transplantation or have already received one will be included in this study. Individuals will undergo a battery of detailed neurocognitive tests at baseline (in part before surgery), and then 3 and 12 months afterwards. Furthermore, the enrolled patients will complete a validated German version of the Cognitive Failure Questionnaire for self-assessment (s-CFQ) as well as the Hospital Anxiety and Depression Scale -Deutsche (HADS-D), a self-report screening instrument with two scales that capture anxiety and depression. In addition, a hair sample will be taken at each measurement time point for the determination of hair cortisol levels as a parameter for the cumulative hypothalamic-pituitary-adrenocortical axis activity over the previous three months. The primary outcome measure will be (a) the effect of kidney transplantation on the cognitive performance up to 12 months after transplantation and (b) the course of cognitive performance following kidney transplantation over time.

Discussion The results of our study have potentially important implications for the prevention and treatment of cognitive impairment in kidney transplant individuals. By increasing our knowledge of the neurocognitive profile and assigning the corresponding deficits, it might be possible to create an individualized training program to positively impact cognitive deficits in kidney transplant patients.

Keywords Kidney transplantation · Cognitive performance · Neuropsychological assessment · Depression · Cognitive profile · Chronic kidney disease

Hristos Karakizlis and Johanna M. Doerr have contributed equally to this work.

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Abbreviations

sCFQ	Questionnaire for self-assessment
CKD	Chronic kidney disease
ESRD	End-stage renal disease
HADS-D	The German version of the Hospital Anxiety and Depression Scale
HPA	Hypothalamic-pituitary-adrenocortical
MCI	Mild cognitive impairment
MMSE	Mini-mental-state-Examination
NAsKiT	Neuropsychological Assessment of Cognitive Impairment in Kidney Transplantation
ROCFT	The Rey-Osterrieth Complex Figure Test
RWT	The "Regensburger Wortflüssigkeitstest
TMT	Trail Mark Test
VLMT	The "verbaler Lern- und Merkfähigkeitstest

Introduction

Kidney transplantation is the preferred therapy for individuals with end-stage renal disease (ESRD). To date, efforts to improve cardiovascular and metabolic parameters after transplantation have been made, but the cognitive aspects of chronic kidney disease (CKD) have been relatively overlooked. Association of cognitive impairment with CKD has been reported over the last decade [1–5]. Several studies suggested a prevalence of cognitive impairment in up to 80% of individuals with CKD [1, 2, 5–9]. It has been demonstrated that individuals showed better cognitive performance after kidney transplantation than dialysis individuals [10] but these individuals are also significantly more likely to be affected by cognitive impairment or dementia than age-matched comparison groups [11–13]. Additionally, kidney transplant recipients with cognitive impairment are also affected by increased mortality [14, 15]. However, the actual prevalence of cognitive impairment in transplant recipients (from deceased and living donor) is unknown. The development of cognitive functioning and the detailed degree (i.e., which cognitive domains are particularly affected) has not yet been well studied in kidney transplant individuals. Previous studies in individuals with end-stage renal disease have shown that executive functions are particularly affected [5].

Cognitive impairments are likely to imply a high individual loss of quality of life and early restriction of self-determination and of therapy adherence, which is highly necessary for treatment. Early detection is of paramount significance so as to take preventive action, assess illness-related grief, and to avoid misunderstandings during medical care [16].

Better knowledge of the prevalence as well as of the course and profile of cognitive impairment is important for designing future studies, which will assess the clinical impact of cognitive impairment and develop management strategies. A limited number of studies have concentrated on the effects of kidney transplantation on cognitive function with divergent results [13].

The goal of our study is to examine (a) the extent of cognitive impairment, (b) the course of cognitive performance in kidney transplant individuals and (c) the profile of cognitive impairment (i.e., if a certain cognitive domain is more affected than others). Furthermore, we explore the impact and temporal course of variables with a potential influence on cognitive performance as secondary research questions. In this context, variables related to stress (subjective stress, depression, and long-term activity of the hypothalamic pituitary adrenal axis (HPA)) are of special interest to us.

Materials and methods

Study design and enrollment

We are conducting a prospective single-center cohort study at the University Hospital Giessen and Marburg, Giessen, Germany. It complies with the Declaration of Helsinki and has been approved by the ethics committee of the Justus Liebig University Giessen (ref 195/20). Written informed consent will be signed by the individuals and by the investigator prior to the patient´s enrollment.

Our study team consists of members of the nephrology, kidney transplantation, neurology and neuropsychology departments.

Inclusion and exclusion criteria

Individuals who are scheduled to receive a kidney transplantation (immediate—deceased kidney donor, or within the following 2 weeks—living kidney donors) or have already received a kidney transplantation in the past will be included in this study. Due to the use of a standardized psychological assessment, individuals have to be native German speakers and at least 18 years of age. individuals under the legal supervision of a caregiver and with preexisting psychiatric disorders will be excluded from the study.

The study is divided into two parts (Table 1).

Part A:

All included individuals undergo a detailed neurocognitive test battery on the day of transplantation (deceased kidney donation), or within 14 days before transplantation (living kidney donation). The neurocognitive test battery will be repeated after 3 and 12 months.

For individuals on the waiting list for deceased donor kidney transplantation we aspire to also carry out neurocognitive tests during standard visits to the hospital. Standard visits are typically several years apart and the date of transplantation is unforeseeable. Therefore, we expect not to be

Table 1 Trial schedule of enrollment and assessments

		Enrollment		Post-allocation	
Study Period, Part A					
Time point		t_{-1}	t_1	t_2	t_3
Enrollment					
Eligibility screen		X			
Informed consent		X			
Allocation		X			
Interventions					
Kidney transplantation			X		
Assessments					
ROCFT		X		X	X
VLMT		X		X	X
TMT-A		X		X	X
WMS-R-numbers forward		X		X	X
TMT-B		X		X	X
WMS-R-numbers backwards		X		X	X
RWT		X		X	X
Study period, Part B					
Time point	t_{-2}		t_{-1}	t_1	t_2
Enrollment					
Eligibility screen			X		
Informed consent			X		
Allocation			X		
Interventions					
Kidney transplantation	X				
Assessments					
ROCFT			X	X	X
VLMT			X	X	X
TMT-A			X	X	X
WMS-R-numbers forward			X	X	X
TMT-B			X	X	X
WMS-R-numbers backwards			X	X	X
RWT			X	X	X

able to gather respective data for the majority of our participants and rather, will use it descriptively and for qualitative analyses.

Part B:

All included individuals who have already undergone transplantation and are in outpatient follow-up will undergo the same neurocognitive test battery as individuals in part A at baseline, after 3 months, and after 12 months.

Neuropsychological assessment

A battery of standardized cognitive tests will be performed at different timepoints (Table 1). Parallel test forms will be used at follow-up to account for learning effects. The order in which the parallel test forms are presented will be counterbalanced so that each parallel test form wil be administered with the same frequency at each test time point.

The cognitive test battery

We first administer the Mini-Mental Status Examination (MMSE) [17] as a neurocognitive screening test, together with a test battery consisting of five tests, assessing the cognitive domains of selective attention, verbal and visual memory with short-delay and long-delay memory conditions, verbal working memory, word fluency and symbol processing. Raw scores are transformed into z-scores adjusted for age, and if available sex, as well as years of education.

The individual's degree of impairment will be stratified using the algorithm adopted by Murray and colleagues [1] based on the Mayo criteria for mild cognitive impairment (MCI) [18] and the Diagnostic and Statistical Manual, fifth Edition, criteria for major neurocognitive impairment as approximate guidelines [19].

Individuals will be classified depending on their extent of impairment and the number of affected domains as.

1. Unimpaired: performance better than 1.5 standard deviations (SD) below the norm sample in any test considered for the classification.
2. Mildly impaired: mild deficits (scores 1.50 to 1.99 SD below the norm sample) in only one domain.
3. moderately impaired: deficits in two domains or a severe deficit (2.0 SD below the norm Sample) in one domain.
4. Severely impaired: deficits in at least two domains.

The domains of executive functions (semantic and phonemic fluency, working memory, and mental flexibility), verbal memory (immediate and delayed recall, recognition), visual memory (delayed recall), and attention (symbol processing speed) are considered in the classification.

For this purpose, we will use the following validated tests (Table 2):

Verbal learning and memory test

To assess verbal memory, the "verbaler Lern- und Merkfähigkeitstest" (VLMT) [20], a modified German version of the Rey Auditory Verbal Learning Test [21] will be administered. This test can be used to evaluate short-term memory, learning, episodic memory and verbal discriminability. First, a list of 15 words is read to the patient by the investigator. The direct retrieval by the patient is scored as short-term memory performance. Second, the patient has to learn the word list in five learning trials. The sum of the recalled words represents a learning parameter. Third, a second word list with new words is presented verbally, and recalled only once for interference. After this, the learned words on the first word list have to be recalled. This is used as a measurement of a short-delayed function of verbal episodic memory. A second verbal episodic memory measurement is performed 20 min later (long delay). Finally, the verbal recognition ability is assessed by discriminating between already learned and new words. Between the short-delayed verbal episodic memory trial and the long-delayed verbal episodic memory trial, nonverbal cognitive tests are performed to avoid the potential effect of interfering words not included in the learned wordlist. Three parallel versions of this test are available and are implemented during baseline and follow-ups in alternating order.

Table 2 The different neurocognitive tests and their affiliation to a particular cognitive domain

Cognitive domain	Test
Visual memory	ROCFT
Verbal memory	VLMT
Attention	TMT A WMS-R–numbers forward
Executive function	TMT B WMS-R–numbers backwards RWT

Rey-Osterrieth Complex Figure Test

In the Rey-Osterrieth Complex Figure Test (ROCFT) [22], the subject is first asked to copy a complex figure (visuo-construction/action planning). After about 30 min, the subject is then asked to draw the figure again from memory (visual memory).

Trail Making Test

Selective attention and cognitive flexibility are examined using the Trail Making Test (TMT) [23]. It consists of subtests A and B. In TMT-A, the patient has to link numbers in ascending order as quickly as possible with a pencil (visual scanning and basal psychomotor speed, selective attention) on a test sheet. TMT-B additionally requires the ability of cognitive flexibility by switching between letters and numbers. The quotient formed from the processing time of subtest B and subtest A (B/A) can be used to represent a measure of cognitive switching ability (serial cognitive flexibility, executive function) independently of any psychomotor slowing.

Wechsler Memory Scale (subtest digit span)

The subject is instructed to repeat successively increasing sequences of numbers forward (memory span, attention) and backward (working memory, executive function) on the "digit span" subtest of the Wechsler Memory Scale—Revised (WMS-R) [24].

Regensburg-word-fluency-test

Semantic and phonemic verbal fluency will be tested using the "Regensburger Wortflüssigkeitstest" (RWT) [25] which also exists in parallel versions. In this test, the patient is asked to name as many words as possible that belong to a specific category (e.g. animals) within 1 min. For the phonemic word fluency subtest, the target is to name as many words as possible within 1 min that begin with a specific letter. This is a test for divergent thinking (executive function).

Possible stress-related mediators and moderators

Anxiety and depression

The HADS-D [26] the German version of the Hospital Anxiety and Depression Scale by Zigmond and Snaith will be administered [27]. It is a standardized self-report screening

instrument with two scales that capture anxiety and depression. Each scale is represented by seven items presented alternately. Each item is scored on a four-point Likert scale. The questions measure the expression of anxious and depressive symptoms referring to the last week. The items of the anxiety scale mainly refer to symptoms such as worry, apprehension, nervousness, and motor tension. The items of the depression scale focus on loss of motivation and interest, reduction of joy, and reduced drive. The questionnaire is well suited for recording reactive disorders in the physically ill. Another advantage is the quick completion time of approximately five minutes.

Self-assessment of cognitive failure

Study individuals will complete a validated German version of the Cognitive Failure Questionnaire for self-assessment (s-CFQ) [28]. It represents a procedure for self-assessment of the frequency of committed everyday errors, in the areas of perception, memory, and action regulation (executive functions). The CFQ has been used, revised, extended, and validated in numerous studies [28, 29].

Stress experience

The Perceived Stress Scale [30] is used to assess subjective stress levels. With 10 items on a scale from "never" (0) to "very often" (4), the scale measures the occurrence of stress (feelings of being overtaxed, loss of control) in the last month. The German translation showed good internal consistency and construct validity [31].

We extended this questionnaire to include stress levels before and after testing prior to planned transplantation by the item "How stressed do you feel at the moment?" (1–10).

This allows us to measure the acute stress level at the beginning and at the end of the cognitive test and thus to investigate the difference in stress levels between the groups as well as the influence of the current stress level on cognitive functions.

Hair cortisol

A hair sample is taken from the included individuals at each measurement time point for the determination of hair cortisol. Two to three thin hair strands are cut as close to the scalp as possible at the position of the posterior vertex. This protocol has been used successfully in studies for over 10 years and is well accepted by study participants [32]. The strands are first preserved and then sent to the laboratory of the Clinical Psychology of Adulthood at the University of Vienna (Prof. Dr. U. M. Nater) for hair cortisol analysis. For the determination of cortisol, commercial immunoassays with chemiluminescent detection (CLIA) from IBL, Hamburg, Germany, are used. For hair cortisol, high test–retest reliability as well as positive correlations with cortisol values from other media (e.g., saliva and urine), and with subjective stress measures are shown [33]. Hair cortisol levels of the first three centimeters from the scalp can be considered a measure of cumulative HPA axis activity over the previous three months [34].

In order to check the influence of steroids on the HPA axis, steroid doses are documented in all patients. Patients do not receive cortisone until transplantation. During transplantation, patients receive a cortisone shot of 1 g prednisolone on the day of transplantation. At the time of discharge from the hospital, the maintenance dose is 10 mg. The dose is usually reduced by 2.5 mg every 3 months and patients are no longer administered cortisone after 12 months. Furthermore, unscheduled intake of cortisone (e.g., during rejection episodes) is documented.

Patient baseline data, comorbidity, laboratory parameters

In addition, baseline patient data, such as age, type of underlying disease, type and duration as well as the dose (*Kt/V*) of the dialysis therapy will be obtained. Comorbidities, that may have an impact on cognitive performance (such as previous stroke, coronary heart disease, hypertension diabetes mellitus, existing dementia or depression), will be documented. Furthermore, blood parameters such as hemoglobin, creatinine, calcium, phosphorus, albumin, triglycerides, cholesterine, urea, pH-value, CO_2, and bicarbonate will be recorded. Current medication data will be obtained from the medical records and by self-report at each testing session. In addition, changes in medication are recorded. The examinations,were executed by trained and certified medical students.

Statistical analysis

This is a within-group design with three measurement time points. We will investigate the proportion (percentage) of individuals that fulfill the above mentioned criteria at each given time point as estimates of prevalence of MCI and major neurocognitive impairment. Furthermore, we will conduct repeated-measures analysis of variance to investigate changes in cognitive performance over time, as well as the influence of different predictors. Cognitive performance of the individuals as a composite score and for each cognitive domain constitutes the dependent variables. The time of measurement and other control variables listed above represent the independent variables. A possible accumulation of the type I error is counteracted by an α-error correction (see below). The partial Eta-squared is calculated as the effect size, and the pairwise post-hoc comparisons are also

corrected for multiple comparisons. The requirement of normal distribution is evaluated by the Kolmogorov–Smirnov test. Variance homogeneity is checked by Levene's test. If the prerequisites for parametric statistics are not fulfilled, a distribution assumption-free covariance analysis according to the Quade model with rank-transformed variables is performed as an alternative.

Further questions are evaluated in terms of exploratory data analysis. Group differences are assessed using the t-test for independent samples or the Mann–Whitney-U test, depending on the scale level. Panels with discrete characteristics are analyzed with the χ^2-test. Measures of correlation for discrete variables represent the contingency coefficients. For continuous characteristics, correlation measures according to Pearson (product-moment correlation) or Spearman (rank correlation) are used depending on the data level, in exceptional cases also according to Kendall (rank correlation without equidistance assumption).

The global significance level is set at $\alpha = 0.05$. A false discovery rate (FDR) is calculated for α-error correction in multiple comparisons [35]. In the stepwise procedure, p-values are ranked in descending order; the null hypothesis is rejected if:

$$p(i) \leq \frac{i}{m}\alpha \tag{1}$$

where m represents the number of p values and i the rank of the p value. Assuming $i = 1$, the FDR is equivalent to the Bonferroni correction.

Sample size calculation

In order to investigate the prevalence of MCI or dementia, all individuals currently registered on the local transplant list, who are able to consent and agree to participate in the study, will be included. Currently, this list includes 142 individuals (75 individuals are in status T (transplantable), 67 individuals are in status NT (non-transplantable).

With regard to outcome measures, previous studies have shown highly significant improvements in some domains after transplantation [36], but have not reported effect sizes or statistical parameters that could be used to calculate effect sizes. Harciarek and colleagues [37, 38] report moderate to strong "time × comparison with healthy controls" interaction effects. We therefore conservatively expect to find low to medium effect sizes. For the detection of low to medium ($f = 0.20$) within-person effects with 3 measurement time points and 2 groups using a repeated-measures ANOVA as explained above, a power ($1 - \beta$ (type II error probability) of 0.80 and a type-I error probability (α) of 0.05, a sample size of 42 is necessary [39, 40]. We therefore aim for a sample size of 50 persons for the follow-up measurements.

Primary outcome measure

The primary outcome measure will be cognitive performance. (a) We will compare cognitive performance before and after kidney transplantation, up to 12 months after transplantation in a population of patients who did not yet receive kidney grafts before enrollment in the study (part A) and (b) we will also investigate the development of cognitive performance over a period of 12 months in a population of patients who already received kidney grafts before enrollment in the study (part B).

Secondary outcome measures

As a secondary outcome, we will assess a distinct profile of cognitive function using standard neurocognitive tests. Furthermore, we will explore the impact and temporal development of a set of risk factors for deficits in cognitive performance. Second, we want to examine the extent to which cognitive impairment affects depression at all follow-up time points. Third, we want to assess how stressors negatively or positively affect cognitive performance. Fourth, we want to investigate to what degree cognitive performance affects the formation and development of donor-specific antibodies.

Discussion

The purpose of this study is to assess the extent and development of cognitive impairment in kidney transplant individuals and to provide a clear profile of cognitive function using standardized neurocognitive tests. Furthermore, we aim to evaluate whether transplantation per se leads to an improvement in cognitive performance.

There is currently no standardized test battery for kidney transplant populations, so we selected different validated tests to evaluate the different domains. Through this, it will be possible to create a neurocognitive profile of the investigated population. The tests used in kidney transplant individuals [10, 11, 41, 42] (Brief Cognitive State Examination, MoCA und 3MS, Modified Mini-Mental State Examination), which can be found in literature, are only screening tests and may underestimate the extent of cognitive impairment. We use a more comprehensive neurocognitive test battery, which is then also able to establish a neurocognitive profile in individuals after kidney transplantation. A recently published study showed a high prevalence of cognitive impairment in dialysis individuals [5], examined by the CERAD Test battery [43].

Anemia, secondary hyperparathyroidism, dialysis disequilibrium and uremic toxins (UT) have been reported as major causes of cognitive impairment accompanied by chronic kidney disease [44], as well as dialysis duration [45].

We assume that these parameters improve after transplantation and want to investigate the effect of these parameters on cognitive function.

Depression in hemodialysis individuals is characterized as one of the most common psychological aspects regarding studies on individuals with kidney failure [46]. To evaluate the frequency of depression and its effect on cognitive performance the HADS-D [26] Test will be performed. We also hypothesize that transplanted individuals suffering from depression display significantly higher cognitive impairment than transplanted individuals without depression. In one of our previous investigations, depression was significantly associated with a lower level of cognition [5]. Other studies have also found similar decline in cognition with the presence of depression [45, 47, 48]. This can be explained by the effects of symptoms of depression on domains of cognition like executive functioning and processing speed [48, 49]. A recent meta-analysis also shows that subjective stress influences the development of cognitive impairment [50].

A likely mediator of the association between stress and cognitive performance, but also between depression and cognitive performance, is HPA axis activity, which is commonly assessed via its end-product cortisol. Excess cortisol has been found to have damaging effects on the limbic system, which leads to impairment of learning mechanisms [51]. Some studies also suggest that higher cortisol levels are associated with slower processing speed in persons suffering from depression [52, 53]. In line with this, one study found a negative association between hair cortisol and cognitive performance after stroke [54]. Hair cortisol as a marker of HPA axis activity is of special interest because it represents the cumulative HPA axis activity of the months before the time point of measurement [33] (in our case, before kidney transplant). However, we are not aware of any study that has investigated associations of subjective stress or hair cortisol, or their interaction with depression, in kidney transplant individuals.

Individuals who received kidneys from a deceased donor as well individuals who received living kidney donation will be investigated. In order to detect an effect of transplantation, testing will be performed close to the time of transplantation. Neurocognitive testing is performed in living kidney donor recipients within 14 days prior to planned transplantation. In individuals receiving postmortem donation, prior scheduling of neurocognitive testing is not possible. After individuals are placed on the waiting list, the waiting period for a deceased donor renal transplant usually ranges between 6 to 8 years in Germany [55] and around 4 years in the Eurotransplant region [56], making testing at listing impractical. Therefore, we decided to perform testing when we admit individuals for kidney transplantation during dialysis prior to transplantation. It has been shown that the test results are not affected by dialysis [57].

Despite vigorous planning, the present investigation certainly contains some limitations. The test environment may not be optimal for the individuals who will receive the kidney from a deceased donor (patient might be more nervous than usual). It would have been more ideal to test those individuals 1 or 2 weeks before transplantation, but this is not possible, as it is not known when these individuals will receive their transplant offers. It seems possible that HADS responses may be influenced by the positive news of the transplantation. Here, however, it is likely that the influence might be more pronounced in individuals for whom transplantation is not planned (deceased donor kidney transplantation) than in those for whom transplantation is planned (living donation).

The results of our study could have potentially important implications for the prevention and treatment of cognitive impairment in kidney transplant individuals. By increasing our knowledge of the neurocognitive profile and assigning the corresponding deficits, it might be possible to create an individualized training program to positively impact cognitive deficits in these individuals.

Trial status

The study is currently enrolling individuals. The local human research ethics committee of the Justus-Liebig-University of Giessen (AZ 195/20) approved this study. Recruitment started in Jan 2021 and is expected to be completed in December 2022. The study was registered with the German clinical Trials register under the number DRKS00029164.

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Availability of data and material The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability No new code was produced in this study.

Declarations

Conflict of interest Each author certifies that he or she, or a member of their immediate family, has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the contents of the submitted article. The results presented in this article have not been published previously in whole or part, except in abstract format.

Ethical approval and consent to participate This study was approved by the ethics committee of the University of Giessen and conforms to

the Declaration of Helsinki. Written informed consent is obtained from of all the participants prior to study enrollment.

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4.4. RETRANSPLANTING A PREVIOUSLY TRANSPLANTED KIDNEY: A SAFE STRATEGY IN TIMES OF ORGAN SHORTAGE? (A4)

Hristos Karakizlis, *Marieke van Rosmalen, Philipp Boide, Ingolf Askevold, Serge Vogelaar, Thomas Lorf, Gabrielle Berlakovich, Martin Nitschke, Winfried Padberg, Rolf Weimer*

Organmangel ist ein Problem von globalem Ausmaß. Die Retransplantation einer zuvor transplantierten Niere könnte vor diesem Hintergrund eine Möglichkeit sein, den Spenderpool zu erweitern. Wir berichten über unsere Erfahrungen mit der erfolgreichen Wiederverwendung von transplantierten Nieren in der Eurotransplant-Region.

Zwischen dem 1. Januar 1995 und dem 31. Dezember 2015 wurde eine Abfrage in der Eurotransplant-Datenbank durchgeführt, um Nierenspender zu finden, die selbst zuvor ein Nierentransplantat erhalten hatten. Die Nierenfunktion wurde beobachtet und bis zum Verlust des Transplantats oder dem Tod des Patienten verfolgt.

9 von insgesamt 68.554 allozierten Nieren waren zuvor transplantiert worden. 4 dieser Nieren wurden schließlich noch einmal transplantiert. Das mittlere Intervall zwischen der ersten Transplantation und dem Angebot einer erneuten Transplantation betrug 1689 ± 1682 Tage (SD; Range 55–5.333 Tage). Zum Zeitpunkt der ersten Transplantation betrug das mittlere Serumkreatinin der Spender 1,0 mg/dl (0,6–1,3 mg/dl) und bei der zweiten Transplantation 1,4 mg/dl (0,8–1,5 mg/dl). Das mittlere Transplantatüberleben lag beim ersten Empfänger bei 50 Monaten (2–110 Monate) und beim zweiten Empfänger bei 111 Monaten (40–215 Monate).

Die Transplantation einer zuvor transplantierten Niere kann mit gut erhaltener Transplantatfunktion und langem Transplantatüberleben erfolgreich durchgeführt werden, selbst wenn die erste Transplantation lange zurückliegt. Solche Organe könnten in sorgfältig ausgewählten Fällen auch bei jüngeren Empfängern in Betracht gezogen werden.

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Retransplanting a previously transplanted kidney: A safe strategy in times of organ shortage?

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Abstract

Background: The shortage of organs for transplantation remains a global problem. The retransplantation of a previously transplanted kidney might be a possibility to expand the pool of donors. We provide our experience with the successful reuse of transplanted kidneys in the Eurotransplant region.

Methods: A query in the Eurotransplant database was performed between January 1, 1995 and December 31, 2015, to find kidney donors who themselves had previously received a kidney graft.

Results: Nine out of a total of 68,554 allocated kidneys had previously been transplanted. Four of these kidneys were transplanted once again. The mean interval between the first transplant and retransplantation was 1689±1682 days (SD; range 55–5,333 days). At the time of the first transplantation the mean serum creatinine of the donors was 1.0 mg/dl (.6–1.3 mg/dl) and at the second transplantation 1.4 mg/dl (.8–1.5 mg/dl). The mean graft survival in the first recipient was 50 months (2–110 months) and in the second recipient 111 months (40–215 months).

Conclusion: Transplantation of a previously transplanted kidney may successfully be performed with well-preserved graft function and long-term graft survival, even if the first transplantation was performed a long time ago. Such organs should be considered even for younger recipients in carefully selected cases.

KEYWORDS
graft survival, kidney injury, organ shortage, retransplantation

1 | INTRODUCTION

Organ shortage is a common problem in the Eurotransplant (ET) region, especially in Germany. The resulting prolonged waiting time on dialysis increases the cardiovascular risk and thereby the mortality rates of our patients.[1] On the one hand, kidney organ shortage may be explained by the increased need for organs due to demographic changes and the aging of the population, thereby resulting in an increased incidence of end stage renal disease (ESRD) and other end stage organ failures.[2] On the other hand, the number of transplanted organs has decreased dramatically in recent years in Germany. In 2019, 1628 kidney grafts were transplanted in Germany and 3191 in the whole ET

region. These are 628 and 540 less organs, respectively, than in 2010.[3] At the end of 2019, 7148 patients were actively waiting on dialysis to receive a kidney transplant in Germany, and 10,723 patients were on the active waiting list in the whole Eurotransplant region.[4] The waiting period for a deceased donor renal transplant usually ranges between 6 and 8 years in Germany[5] and around 4 years in the Eurotransplant region.[4]

Due to the urgent need to raise the renal transplant rate, new options of donation have already been realized, such as using living renal transplantation across ABO or positive crossmatch barriers,[6–10] kidney exchange programs for living transplantation[7,11] and extending the deceased donor pool by increased utilization of so-called marginal donors. With regard to the latter option, deceased donor renal transplantation by the Eurotransplant senior program,[2,12] double kidney transplantation[13] or even using kidneys with severe acute renal failure[14,15] have been successfully realized.

Another option is the transplantation of a previously transplanted kidney when a deceased donor presents a well-functioning renal allograft.[16–21] This option is hardly used at the moment, but might be a possibility to expand the pool of donors. The question is whether this procedure may be a safe option in times of organ shortage or whether special prerequisites such as good renal function without an extended time frame since the previous transplantation should be fulfilled for successful retransplantation of a previously transplanted kidney. A longer time period since the previous transplantation of the graft might be associated with significant chronic changes, which may not be reflected by serum creatinine or eGFR of the donor, but may compromise graft outcome after another transplantation. We provide our experience of the successful reuse of transplanted kidneys in the Eurotransplant region.

2 | METHODS

With institutional review board approval by the ethics committee of the University of Giessen (AZ 126/21), we conducted a query in the Eurotransplant database between January 1, 1995 and December 31, 2015, comparing the parameters ABO blood group, sex, HLA antigens, and date of birth between the kidney recipients and kidney donors in order to detect those kidney donors who previously received a renal transplant. The numbers of offered and finally accepted kidney grafts for retransplantation were analyzed, as well as the reasons for refusal of such kidney grafts.

Regarding the first recipient of a kidney graft (who is the current donor), we collected data on age, sex, weight, graft survival, graft function (serum creatinine, BUN eGFR measured by CKD-EPI and proteinuria), cause of death, and whether a right or left kidney was transplanted. With regard to the second and thus current recipient of the kidney graft, we collected data on age, sex, weight, graft function (serum creatinine, BUN, eGFR measured by CKD-EPI and proteinuria) and graft survival, cause of graft loss and cause of death). Furthermore, the interval between the first and the second transplantation was recorded as well as the immunosuppressive regimen of the second kidney graft recipient. We observed and followed-up on the second graft recipients until graft loss or the patient's demise. The data on episodes of graft rejection and biopsy findings (as far as available) were collected.

Statistics. Mean, standard deviation (SD), and range are given. Comparisons between the rejected and accepted renal grafts were conducted with Mann-Whitney test. P values $< .05$ were considered significant.

3 | RESULTS

Between January 1, 1995 and December 31, 2015, a total of 68,554 kidneys were allocated for transplantation in the Eurotransplant region. Nine of these kidneys (.00013%) had been previously transplanted and were offered to be transplanted once again. Four out of these nine kidneys (.000006%) were eventually transplanted again. Two of these were left kidneys and two were right kidneys. By reviewing the rejected donor data, the likely reasons of rejection of the kidneys were decreased kidney function, severe arteriosclerosis of the graft arteries and chronic hepatitis (Table 2).

The mean interval between first transplantation of the renal graft and retransplantation offer was 1689±1682 (SD) days (range 55–5333 days). As shown in Table 1, the mean age of the first donor was 32 years (range 18–54), and of the first recipient 49 years (range 32–61) at the time of this first transplantation. The mean age of the second donor was 53 years (range 37–67), and of the second recipient 66 years (range 65–67). However, the mean age of the graft at the time point of retransplantation was 36 years (range 23–54) and thus younger than the mean age of the current donor.

At the time of the first transplantation mean serum creatinine of the donor was 1.0 mg/dl (range .6–1.3) with a mean eGFR of 87 ml/min (range 68–114). At the time of the second transplantation mean serum creatinine level of the donor was 1.4 mg/dl (range .8–1.5) with a mean eGFR of 55 (range 37–76). Considering that the second donor had only one functioning kidney, graft function appeared somewhat better compared to the first donor in 3 of the 4 cases (Table 1). The average time between the first transplantation and death of the first recipient was 50 months (range 2–110). The mean graft survival time in the second recipient was 111 months (range 40–215) (Figure 1).

Regarding age, renal function measured by serum creatinine and eGFR at the time of the first transplant and the second transplant, and graft survival in the first recipient, there were no statistically significant differences between the accepted and rejected offers (Table 2). In the following, we report details of the four cases with retransplanted kidneys (Figures 1 and 2).

3.1 | Case 1

In July 1993, the kidney of a 36-year-old woman was first transplanted into a 43-year-old man. The first donor died after cerebrovascular

TABLE 1 Characteristics of the accepted first and second grafts

	Case 1	Case 2	Case 3	Case 4
First donor at time of transplantation				
age (year)	36	54	18	20
serum creatinine (mg/dl)	1.1	.6	1.3	1.2
eGFR (CKD-EPI) (ml/min/1.73m^2)	68	114	80	87
cause of death	CVA	CVA	suicide (head injury)	polytrauma
weight (kg)	65	97	70	67
sex	female	male	male	male
right / left kidney transplanted	left	right	left	right
Second donor (first recipient)				
age (year) at time of the first transplantation	43	61	32	59
serum creatinine (mg/dl)	1.5	1.5	1.3	.8
eGFR (CKD-EPI) (ml/min/1.73m^2)	55	37	52	76
cause of death	CVA	CVA	CVA	cerebral infarction
weight (kg)	84	60	50	70
sex	male	female	female	female
age (year) at time of retransplantation	45	61	37	67
total age of the transplanted kidney at time of retransplantation	38	54	24	29
CIT second transplantation (h and min)	15h06min	3h50min	7h47min	10h12min
Operation time second transplantation	n.a.	2h30min	n.a.	2h31min
Delayed graft function[a]	no	no	no	yes
Age of the second recipient (year) at time of transplantation	65	65	65	67
Graft survival in the first recipient (months)	25	2	63	110
Graft survival in the second recipient (months)	215	125	63	40
other organs transplanted from this donor	none	none	liver	right lung, liver
Immunosuppressive treatment (second recipient)				
induction therapy maintenance immunosuppression	None tacrolimus prednisolone	None CyA, MMF prednisolone	Basiliximab CyA prednisolone	Basiliximab tacrolimus, MMF prednisolone

Abbreviations: CVA, cerebrovascular accident, otherwise not specified; CyA, cyclosporine A; eGFR, estimated glomerular filtration rate calculated by CKD-EPI; kg: kilogram; MMF, mycophenolate mofetil; n.a., data not available; y, years.
[a]Defined by at least one postoperative dialysis treatment.

accident with an excellent serum creatinine of 1.1 mg/dl and BUN of 10.3 mg/dl. The eGFR was 68 ml/min/1.73m^2. In September 1995, the first recipient of the kidney graft also died after a cerebrovascular accident. At the time of death, graft function had deteriorated to a serum creatinine of 1.5 mg/dl and an eGFR of 55 ml/min/1.73m^2. Subsequently, the kidney was retransplanted into a 65-year-old patient. Immunosuppression consisted of tacrolimus and prednisolone without antibody induction therapy. The graft function improved after transplantation and remained excellent following hospital discharge until the patient passed away. According to the patient's last examination in August 2013 (7 days before death due to cardiac arrest after an accident), the graft function of the now 83-year-old patient was still excellent with a serum creatinine value of 1.2 mg/dl with proteinuria probably in the normal range (30 mg/dl).

3.2 | Case 2

This kidney was first transplanted into a 61-year-old recipient in September 1998. The donor was a 54-year-old man who died due to a cerebrovascular accident. The kidney function of the first donor was excellent with a serum creatinine of .6 mg/dl and BUN of 6.1 mg/dl. The estimated GFR was 114 ml/min/1.73m^2. Two months after the successful transplantation the recipient died of a cerebrovascular accident and became the second donor of the kidney graft in November 1998. Compared to the point in time of the first transplantation, the renal function had deteriorated to a serum creatinine of 1.5 mg/dl (eGFR 37 ml/min/1.73m^2) and BUN of 9.3 mg/dl. Immunosuppression of the 66-year-old second recipient of the graft consisted of cyclosporine A, mycophenolate mofetil and prednisolone without antibody induction

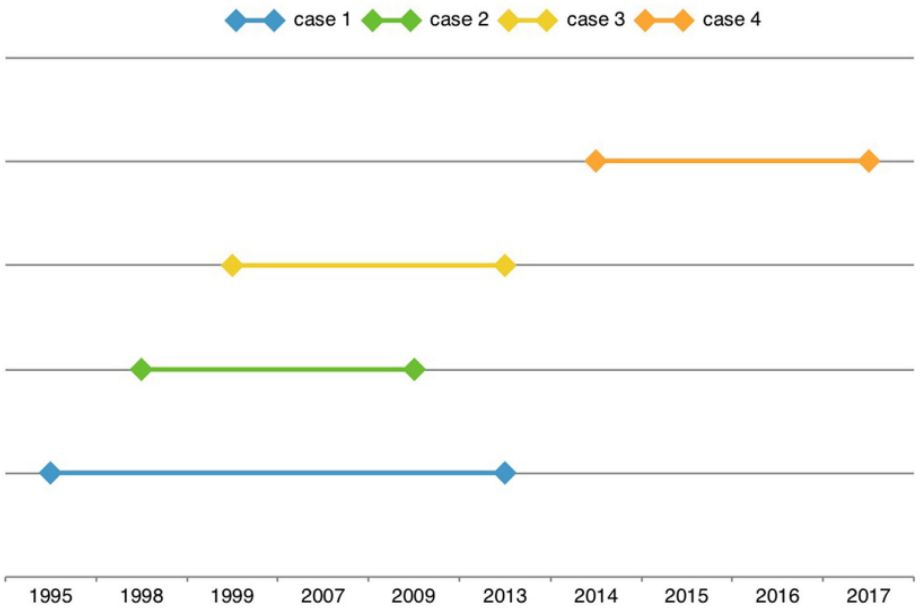

FIGURE 1 Four retransplantations of already previously transplanted kidneys were performed in the Eurotransplant region between 1995 and 2015. For each case, the time period between retransplantation of the graft and graft failure is given

therapy. On the 12th post transplant day a first biopsy was administered and rejection therapy with ATG and prednisolone was given due to suspected acute rejection which, however, could histologically not be confirmed. One month later, in December 1998, a second kidney biopsy was performed because of an increased level of serum creatinine. A tubulointerstitial rejection (BANFF I) according to the BANFF 1995 classification[22] was detected and treated with a methylprednisolone pulse therapy. At the time of the discharge from hospital, the patient presented a serum creatinine level of 1.8 mg/dl. Until 2008 the transplant function was excellent with serum creatinine values between 1.3 mg/dl and 1.6 mg/dl and with proteinuria in the normal range. From the beginning of 2009, however, serum creatinine rose up to > 2 mg/dl. In December 2009, proteinuria started to increase from 150 mg/dl to 500 mg/dl. In January 2010, the patient lost graft function and hemodialysis treatment was initiated. A biopsy was not performed, and as a result a chronic humoral rejection could not be confirmed. The patient died of pneumonia at the age of 77 in December 2011.

3.3 | Case 3

The first transplantation from an ideal 18-year-old donor, who died due to a head injury by suicide, took place in May 1994. The first recipient was a 32-year-old woman. The kidney function at the time of the first transplantation of the graft was good with a serum creatinine of 1.3 mg/dl. The eGFR was 80 ml/min/1.73m^2. The first recipient died due to a cerebrovascular accident in August 1999, and became donor to the second 65-year-old recipient. Graft function at that time was good with a serum creatinine of 1.3 mg/dl (eGFR of 52 ml/min/1.73m^2). The Immunosuppression given to the second graft recipient consisted of cyclosporine A and prednisolone with basiliximab induction. Transplant function was excellent until December 2005, with a serum creatinine of 1.2 mg/dl without episodes of rejection. At the same time a significant proteinuria was detected (1000 mg/g creatinine). 8 years after the transplantation the patient was diagnosed with non-Hodgkin lymphoma and mamma carcinoma. Chemotherapy was initiated and cyclosporine A treatment was stopped. In December 2007, recurrent infections (CMV, EBV) and chemotherapy for non-Hodgkin lymphoma with discontinuation of cyclosporine A treatment probably led to transplant failure. The patient died in October 2010 aged 77 years due to PTLD progress and mamma carcinoma (first diagnosed in 2005).

3.4 | Case 4

The first kidney transplantation was performed in January 2005 from an ideal donor who was 20 years old and died after polytrauma with a serum creatinine value at time of donation of 1.2 mg/dl and an eGFR of 87 ml/min/1.73m^2. There was only one mismatch in the HLA antigens (HLA-A/B/C/DR/DQ) between donor and recipient. The first recipient was a 59-year-old woman with suspected chronic glomerulonephritis as cause of ESRD. The first recipient died after ischemic cerebral infarction in March 2014. The last examination (11/2013) showed good graft function with a serum creatinine of 1.0 mg/dl, eGFR of 61 ml/min/1.73m^2 and proteinuria of 90 mg/24h. The pre-donation kidney function was well preserved with a serum creatinine level of

TABLE 2 Characteristics of the rejected grafts

	Case 1	Case 2	Case 3	Case 4	Case 5	mean (sig)
first donor at time of transplantation						
age (year)	51	36	64	42	59	50 (*P* .110)[a]
serum creatinine (mg/dl)	2.0	1.4	0.9	1.8	1.1	1,4 (*P* .286)[a]
eGFR (CKD-EPI) (ml/min/1.73m^2)	29	48	84	34	55	50 (*P* .063)[a]
cause of death	SAB	SAB	ICB	SAB	ICB	
weight (kg)	80	80	65	83	85	
sex	female	female	female	female	male	
right / left kidney transplanted	left	left	left	left	left	
Second donor (first recipient)						
age (year) at time of the first transplantation	48	56	60	68	56	58 (*P* .566)[a]
serum creatinine (mg/dl)	2.1	1.9	1.0	1.4	1.4	1.6 (*P* .550)[a]
eGFR (CKD-EPI) (ml/min)	27	39	86	49	38	48 (*P* .550)[a]
cause of death	ICB	ICB	ICB	SAB	ICB	
weight (kg)	85	105	70	90	75	
sex	female	male	male	male	female	
age (year) at time of retransplantation	50	58	61	73	71	60 (*P* .19)[a]
Immunosuppressive treatment (first recipient)	MMF sirolimus	not known	MMF everolimus	CyA MMF prednisolone	Tacrolimus prednisolone	
Graft survival in the first recipient (months)	22	33	15	54	177	60 (*P* .190)[a]
suspected reason for rejection	probably marginal kidney function	probably marginal kidney function	Status post gastric cancer	severe arteriosclerosis of graft arteries	acute kidney injury and chronic hepatitis B	

Abbreviations: ICB, intracerebral hemorrhage; SAB, subarachnoid hemorrhage; CyA, cyclosporine A; eGFR, estimated glomerular filtration rate calculated by CKD-EPI; kg, kilogram; MMF, mycophenolate mofetil; y, years.
[a]Compared with the accepted offers.

.8 mg/dl and an eGFR of 76 ml/min/1.73m^2 at the time of the second transplantation.

The second recipient was a 67-year-old patient with ESRD due to IgA nephropathy, who was transplanted in March 2014. Graft function was delayed (one post-transplant dialysis) but reached an averaged serum creatinine of 2.6 mg/dl, a measured creatinine clearance of 30 ml/min 1-year posttransplant, without acute rejection episodes. Immunosuppression consisted of tacrolimus, mycophenolate and prednisolone with basiliximab induction. The 4- and 12-month protocol biopsies showed a reactive focal segmental and focal global glomerulosclerosis (4/13 glomeruli in both biopsies) and a 20% chronic tubulointerstitial damage without signs of rejection or cyclosporine toxicity. At that time graft function was stable with a serum creatinine of 2.5 mg/dl.

Thirty-six months after transplantation, hepatitis E was detected associated with ascites formation and significant deterioration of renal function. Immunosuppression with mycophenolate was stopped and because of persistent hepatitis E ribavirin treatment was initiated. Over time, liver cirrhosis CHILD B with ascites and esophageal varices was developed. Within a year, there was a further deterioration in kidney function (serum creatinine between 3.5 mg/dl and 4.4 mg/dl) due to recurrent liver decompensation. In July 2017, hemodialysis was restarted. The patient is still alive.

These data of four recipients of a previously transplanted kidney show a satisfying graft survival rate between 3 and 18 years (case 1 with 6570 days [18 years], case 2 with 3801 days [10 years 5 months], case 3 with 3034 days [8 years 4 months], case 4 with 1075 days [3 years]). All cases demonstrated an immediate functional recovery of the graft without the need for postoperative dialysis therapy.

4 | DISCUSSION

Kidney transplantation remains the preferred therapy for patients with ESRD. However, it is limited by the shortage of kidney donations. Despite attempts to increase the number of deceased and living donors, success has been limited. In times of organ shortage new ways should be found to expand the pool of available organs. The reuse of a

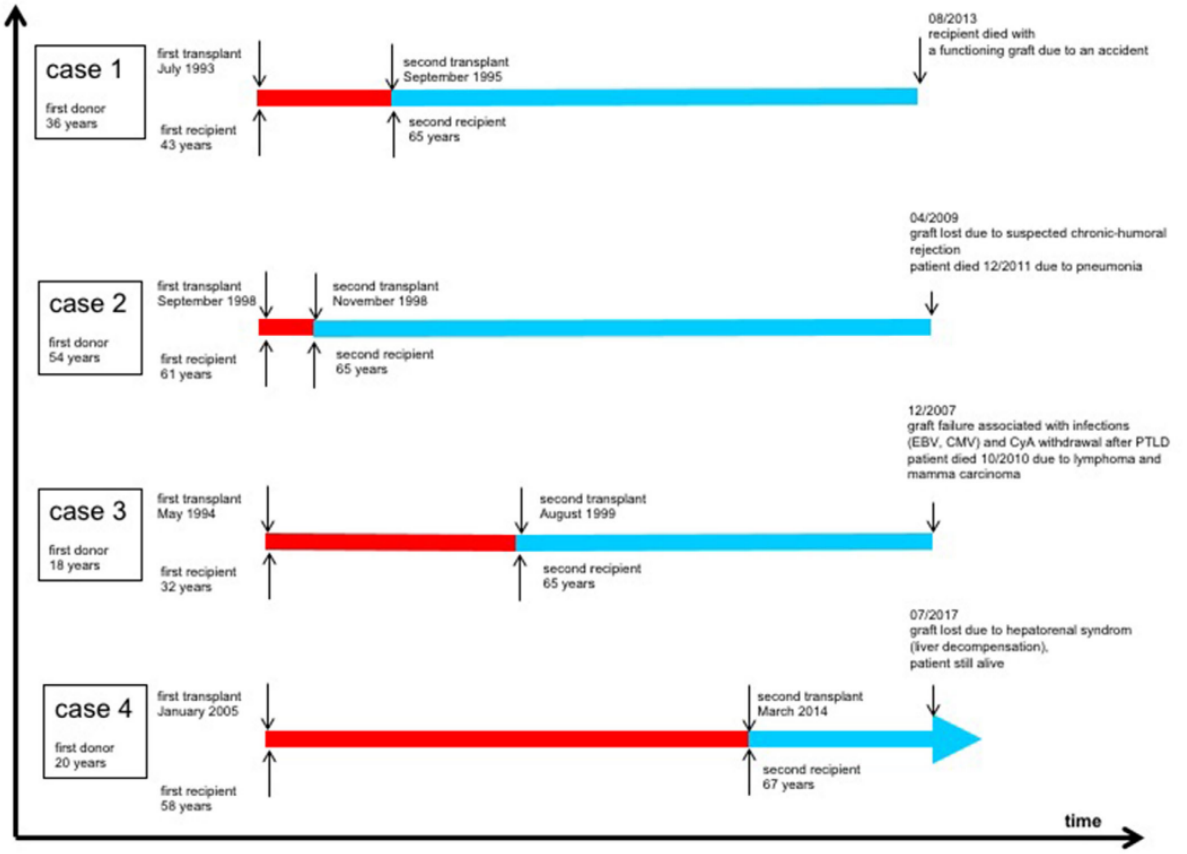

FIGURE 2 Time course of the four renal transplantations. The x axis indicates the time span of graft survival in the first recipient in red, and the time span of graft survival in the second recipient in blue. Labeling shows the dates of the transplantations and the ages of the individual recipients and donors at this time point, as well as the reason of graft failure or patient death in the second recipient. CMV: cytomegalovirus; EBV: Epstein-Barr virus; GN: Glomerulonephritis; PTLD: post-transplant lymphoproliferative disorders; CyA: cyclosporine A

transplanted kidney might be such an approach. As the most common cause of renal allograft loss is death of the patient with a functioning graft,[23] there might be a relevant potential to increase the number of donated kidneys. Ojo et al.[24] analyzed data of the UNOS Scientific Renal Transplant Registry in combination with ESRD patient data in the United States Renal Data System (USRDS) of all renal transplant recipients over 18 years of age from 1987 to 1996 (n = 86,502) and found that 21% of these patients (n = 18,482) died and 38.1% of those patients deceased (n = 7040) with a functioning graft. Veale et al.[25] investigated the period between 2005 and 2014 in the US and were able to prove that every decade about 20–25% of kidney recipients died with a functioning graft. Qiu et al.[26] examined the frequency of death with a functioning graft (DWF) in the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) database between 1988 and 2004 (n = 207,670) and found out, that the percentage of DWF was 3% in the first posttransplant year and 6.5% yearly in the 2nd to 5th year posttransplant. The occurrence of DWF increased significantly with advancing recipient age among both deceased and living donor kidney recipients. These data provide evidence of a significantly underused pool of deceased donor kidneys.

Our data show that patients who have already been transplanted are rarely considered as donors again. Maybe the awareness has not yet been raised to consider such organs as transplantable, either in the donor center, so that the organs are not allocated at all, or in the potential recipient center having concerns about chronic histological impairment which might comprise success of retransplantation. Although DWF is a common event, not all patients who die with a functioning graft are suitable donors. Patients who die outside of the hospital and multimorbid patients are usually not eligible for organ donation. The potential number of DWF patients eligible for another transplantation of the same kidney graft is further reduced by the following facts. The five most common causes of death in patients with a functioning graft are cardiovascular events, infections, tumors, cerebrovascular diseases, and bleeding.[26] West et al.[27] found out that 22% of those patients die from infection, 17% from myocardial infarction, and 15% from sudden death. Patients who died of active malignant tumor disease or active infection, such as meningitis or HIV, are not

potential candidates for kidney donation. Despite these many limitations, one would assume a greater number of eligible DWF donors in the ET region between 1995 and 2015 than the nine patients reported by us. Although more specified data on this topic are lacking, potential candidates for retransplantation of a previously transplanted kidney may not be taken into account in our intensive care units. Thus, data regarding this problem should be collected by the national organ donation organizations and efforts should be increased to educate on this topic in the intensive care units.

The data of our four realized cases show that even kidneys that already have been transplanted for a long time may be transplanted successfully again into another recipient after brain death of the first recipient.

In the past, this possibility has been rarely used. Only a few cases of transplanting a previously transplanted kidney are published.[17–21,25,28–30] Furthermore, long-term implications of such a retransplantation are not well known. In some reports there were only short-term outcomes described until 1 year posttransplant,[20,25,30] some reports had a follow up of 1–4 years.[18,19,28] Two case reports showed a successful reuse of a transplanted kidney with a follow-up of 5 years[21] and 12 years,[29] respectively, and all published cases had a good graft function in their follow-up time.

Whether the length of graft survival has an influence on graft survival after retransplantation is not clear. For the first time, our case reports have a follow-up period until the second recipient is required to undergo dialysis again or dies. Indeed, Figure 2 of our report indicates that kidney graft survival might be influenced by how long the first graft survived in the first recipient. However, in case 3 PTLD appeared to play a major role and in case 4 hepatorenal syndrome was suspected to cause graft failure, so that a relation between graft survival time after the first transplantation and graft survival after retransplantation of the same graft may not be shown by our data. Furthermore, reliable histological data are lacking which might show an increase in chronic damage associated with graft survival after the first transplantation.

In the few cases reported in literature, the time of graft function in the first recipient does not seem to have a clear influence on the graft survival in the second recipient. However, the follow-up in many case reports was only short. There were only three case reports with a long-term follow up of 12 years,[29] 5 years,[21] and 4 years,[19] respectively, which showed a long and good graft function (serum creatinine 1.3 mg/dl) also in the second recipient despite a longer lasting graft survival after the first transplantation (9 years,[19] 8 years,[21] and 6 years[29]). Another patient was described with a graft survival of 5 years after a survival of the same graft in a previous recipient for only 8 days (brain death due to intracranial hemorrhage).[30]

Our data show that the transplantation of a kidney that has previously been transplanted may be successful. To our knowledge, no report has been published in which the re-transplantation of a previously transplanted kidney was not successful. Our data from Eurotransplant with four successful transplantations and graft survival times between 3 and 18 years confirm this assumption, although a publication bias in regions outside Eurotransplant may be possible. Compared with the accepted organs, it is noticeable that the eGfR of the rejected organs in the ET region at the time of the second offer is lower (not statistically significant). However, it also reveals that the kidney functions were already lower overall at the time of the first transplantation. Thus, low eGFR may not be used as the only reason to reject the organ for re-transplantation.

Important to know are potential risk factors for an unfavorable outcome, when accepting or rejecting organ offers. In principle, extensive scar tissue can make surgical access difficult for a retransplantation. Scar tissue could be avoided by creating wide margins around the allograft.[25] During procurement it must be secured that the renal vessels are flushed. This means that an additional canula might be placed not only in the aorta but in the iliac artery. Then a patch of the donor iliac artery and vein has to be taken to maintain the original vessel length. In the presence of adhesions around the initial anastomosis the vessels must not be dissected. Furthermore, by trimming the iliac patch on the artery and vein, a larger volume vessel anastomosis could be created. Because the renal vessels have already been once dissected, re-grafting could result in further shortening of these vessels. Depending on the adhesions the ureter can be shortened or like in childrens' transplantations used with a bladder cuff. Due to anatomical reasons regarding the blood supply of the ureter this might result in a higher complication rate as insufficiencies or stenosis.

It has to be considered that progression of senescence after retransplantation of a previously transplanted kidney may be accelerated due to repeated ischemia reperfusion injury especially in grafts that have undergone chronic damage after the first transplantation.[31,32] The retransplanted kidneys in our cases were rather young at the time of the retransplantation and thus may better cope with oxidative stress and acute kidney injury posttransplant than older kidneys.[33] However, it appears difficult to predict the extent of the existing chronic damage of an already transplanted kidney at the time of such an organ offer without performing a biopsy. On the other hand, despite the widespread use of pre-implantation biopsies, there is no consensus on their value in predicting allograft survival.[34,35]

Regarding the ideal donor data of the original donor in case 4, a 20% chronic tubulo-interstitial damage 4 and 12 months after retransplantation of this graft seems not adequate and shows that a well preserved pre-donation kidney function 9 years after the first transplantation (serum creatinine of 1.0 mg/dl, measured creatinine clearance of 49 ml/min, proteinuria within the normal range 4 months before donation) does not necessarily indicate the rate of chronic tissue damage despite a nearly full HLA A/B/C/DR/DQ match. Furthermore, chronic changes in kidney grafts are common (29% of the grafts after ½–1 year with a gradual increase to 63% after 10 years[36]).

As the collected data of graft outcome in our series and also in the published case reports[16–21,25,30] are satisfactory, we suggest that the offer of an already transplanted kidney should be carefully considered, especially in case of rather young first donors with currently good graft function of the first recipient. Even with normal serum creatinine and in the absence of proteinuria and albuminuria, a graft biopsy should be mandatory prior to transplantation to rule out major chronic damage. The fact that a kidney has already been transplanted for a long time should not necessarily be a reason to reject such a graft.

As retransplanted grafts may survive for a long time in the new recipient, such organs should not in general be considered for older recipients only, but also for younger ones in carefully selected cases.

Although a high percentage of patients with functioning transplants die, many of them can unfortunately not be considered as organ donors. The reasons are manifold. One is impaired renal function due to chronic damage to the graft, technical difficulties in harvesting the transplanted kidney and the increased risk of infection and/or neoplasm transmission from an immunocompromised donor.

In conclusion, the donation of a previously transplanted kidney to another recipient has received little attention so far and has been performed infrequently. Our report shows that retransplantation of a kidney graft may successfully be performed, even if the first transplantation was long ago. However, careful consideration of the donor (first and second donor) data appears to be necessary in order to exclude major chronic injury. As the potential to perform such retransplantations appears to be underused, efforts should be made to focus on such donations, both in the donor centers to make aware the feasibility, and also in the transplant centers to increase the acceptance of these grafts after careful consideration. However, it must also be realized that the above points, due to the low number of cases, can only be considered in addition to the other multi-faceted approaches.

CONFLICTS OF INTEREST

The authors of this manuscript have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Study concept and design: Hristos Karakizlis (HK), Philipp Boide (PB) and Rolf Weimer (RW). *Acquisition of data*: Hristos Karakizlis (HK), Marieke van Rosmalen (MR), Philipp Boide (PB), Ingolf Askevold (IA), Serge Vogelaar (SV), Thomas Lorf (TL), Gabrielle Berlakovich (GB), Martin Nitschke (MN), Winfried Padberg (WP) and Rolf Weimer (RW). Statistical analysis: HK. Analysis and interpretation of data: HK, MR, RW, IA, PB. Drafting of the manuscript: HK, RW, WP, IA. Critical revision of the manuscript: MR, PB, IA, SV, TL, GB, MN, WP, RW.

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DATA AVAILABILITY STATEMENT

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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4.5. DATA ON IMMUNOGENICITY AND REACTOGENICITY TO COVID-19 VACCINATION AMONG PATIENTS RECEIVING MAINTENANCE DIALYSIS (A5)

Hristos Karakizlis, *Christian Nahrgang, Kevin Strecker, Jiangping Chen, Mostafa Aly, Heiko Slanina, Christian G. Schüttler, Isla Esso, Martin Wolter, Darina Todorova, Sönke Jessen, Andrea Adamik, Claudio Ronco, Werner Seeger, Rolf Weimer, Martina Sester, Horst-Walter Birk, Faeq Husain-Syed*

Im Vergleich zur Allgemeinbevölkerung haben Patienten, die eine Dialysetherapie erhalten, ein erhöhtes Risiko für Morbidität und Mortalität im Zusammenhang mit einer Coronaviruserkrankung-2019 (COVID-19). Derzeit gibt es nur wenige Daten über die spezifische Immunität gegen das schwere akute respiratorische Syndrom des Coronavirus Typ 2 (SARS-CoV-2) nach Impfung bei Dialysepatienten. Die Wirksamkeit der Impfstoffe in dieser Bevölkerungsgruppe wurde nicht explizit getestet, weil sie in der Regel von den SARS-CoV-2-Impfstudien ausgeschlossen wurden. Im Folgenden werden Daten zu den spezifischen zellulären (Interferon-γ- und Interleukin-2-ELISpot-Assays) und humoralen Immunantworten (Dot-Plot-Array und Chemilumineszenz-Mikropartikel-Immunoassay) 4 und 6 Wochen nach einer Einzeldosis oder einer vollständigen homologen Doppeldosis des SARS-CoV-2-Impfstoffs bei 60 erwachsenen Patienten an der Dialyse (6 davon mit einer Vorgeschichte von COVID-19) vorgestellt. Die Daten wurden im Rahmen eines Projekts gewonnen, das darauf abzielte, a) die Immunreaktion nach einer vollständigen Impfung zu quantifizieren, b) die kurzfristige Dauerhaftigkeit der Immunreaktion zu bewerten und c) die Reaktogenität von SARS-CoV-2-Impfschemata bei Patienten, die an einer Dialysebehandlung teilnehmen, zu untersuchen.

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Data Article

Data on immunogenicity and reactogenicity to COVID-19 vaccination among patients receiving maintenance dialysis

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ABSTRACT

Compared with the general population, patients receiving maintenance dialysis are at increased risk for morbidity and mortality associated with coronavirus disease 2019 (COVID-19). Currently, data on severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)-specific immunity post-vaccination in patients on maintenance dialysis are scarce given that the effectiveness of the vaccines has not been explicitly tested in this population due to their common exclusion from SARS-CoV-2 vaccination trials. We herein present data of the specific cellular (interferon-γ and interleukin-2 ELISpot assays) and humoral immune responses (dot plot array and chemiluminescent microparticle immunoassay) at 4 weeks and 6 weeks following a single dose or a complete homologous dual dose SARS-CoV-2 vaccine regimen in 60 adult patients on maintenance dialysis (six with a history of COVID-19). The data was produced in a framework of a project focused on a) quantifying the immune response after full vaccination, b) evaluating the short-term durability of immune response, and c) examining the reactogenicity of SARS-CoV-2 vaccine regimens in patients on maintenance dialysis.

Specifications Table

Subject	Health and medical sciences: Nephrology
Specific subject area	Chronic kidney disease; kidney failure; SARS-CoV-2; vaccination.
Type of data	Figure
How the data were acquired	The data were acquired via FluoroSpot Immune assay kit, dot plot array, chemiluminescent microparticle immunoassay, and a survey.
Data format	Analyzed Raw
Description of data collection	Blood samples were obtained prior to dialysis treatment at 4 weeks and 6 weeks after complete vaccination. Reactogenicity data were self-reported using a standardized questionnaire. The data were merged from the University Hospital Giessen medical records, the questionnaires, and the immune response data from GenID and Excel 2019 was used to build a database. No imputation was performed for missing data. Outliers were double-checked with medical records before pursuing data analysis. Access to the electronic database was limited to the study investigators.
Data source location	• Institution: University Hospital Giessen and Marburg, Patienten-Heimversorgung outpatient dialysis center • City/Town/Region: GiessenCountry: Germany
Data accessibility	Repository name: Data on immunogenicity and reactogenicity to COVID-19 vaccination among patients receiving maintenance dialysis Data identification number (permanent identifier, i.e. DOI number): 10.17632/dv2vm47sbm.4 Direct link to the dataset: http://dx.doi.org/10.17632/dv2vm47sbm.4
Related research article	Karakizlis H, Nahrgang C, Strecker K, Chen J, Aly M, Slanina H, Schüttler CG, Esso I, Wolter M, Todorova D, Jessen S, Adamik A, Ronco C, Seeger W, Weimer R, Sester M, Birk HW, Husain-Syed F. Immunogenicity and reactogenicity of homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimens in patients receiving maintenance dialysis. Clin Immunol. 2022 Mar;236:108,961.

Value of the Data

- Data on SARS-CoV-2-specific cellular and humoral immunity post-vaccination in patients on maintenance dialysis are scarce. We herein provide data on the cellular and humoral immune responses after full SARS-CoV-2 vaccination obtained in a single-center in Germany. These data could be used to compare immunogenicity to COVID-19 vaccination among different populations.
- Researchers and clinicians aiming to understand the determinants of immune responses after full SARS-CoV-2 vaccination can profit from this dataset. The data is also valuable to researchers who would like to compare our results with other studies on COVID-19 vaccine efficacy from other countries, as well as to researchers who want to perform a systematic review and meta-analysis study in the future.
- The dataset and the questionnaire elaborated may be used by other researchers who aim to conduct similar studies in patients on maintenance dialysis.

1. Data Description

Patients receiving maintenance dialysis are at increased risk for morbidity and mortality associated with coronavirus disease 2019 (COVID-19) compared with the general population [1,2]. Optimizing the vaccination strategy in this population requires an understanding of the humoral and cellular immune response dynamics to SARS-CoV-2 vaccines, but data on SARS-CoV-2-specific immunity post-vaccination in patients on maintenance dialysis are scarce [3]. The data file shared in the repository contains the raw data on our recently published work [4] evaluating the humoral and cellular immunogenicity and reactogenicity of a homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimen in 60 patients receiving maintenance dialysis (six with a history of COVID-19). Data include information on demographics, comorbidities, dialysis modality and vintage, baseline clinical data, and vaccine regimen. The data file also includes data on the SARS-CoV-2-specific interleukin-2 (IL-2) reactivity and interferon-γ (IFN-γ) reactivity at 4 weeks and 6 weeks following a single dose or a complete homologous dual dose SARS-CoV-2 vaccine regimen, and on the self-reported local and systemic adverse events after the first and second dose using a standardized questionnaire (available at: http://dx.doi.org/10.17632/dv2vm47sbm.4).

2. Experimental Design, Materials and Methods

In this study, we investigated the humoral and cellular immunogenicity and reactogenicity of a homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimen in patients receiving thrice-weekly in-center maintenance dialysis (hemodialysis and peritoneal dialysis). At the time of enrollment, the Patienten-Heimversorgung (PHV) outpatient dialysis center located at University Hospital Giessen and Marburg, Giessen, Germany served 84 hemodialysis patients and 5 peritoneal dialysis patients. Patients were approached during their dialysis session for possible participation in the study. Inclusion criteria were: i) recipient of a homologous mRNA-based or a single-dose or homologous dual dose vector-based vaccine regimen (with or without history of COVID-19), and ii) no laboratory evidence of current SARS-CoV-2 infection. All blood samples were obtained prior to dialysis treatment to minimize the risk of leukocyte adhesion to the hemofilter at 4 weeks (T1) and 6 weeks (T2) after complete vaccination, with a tolerance range of ± 2 days. The SARS-CoV-2-specific cellular immune response was evaluated using IFN-γ and IL-2 ELISpot (enzyme-linked immune adsorbent spot) assays as recently described [5,6]. The SARS-CoV-2-specific humoral immune response was evaluated using a dot plot array and a chemiluminescent microparticle immunoassay. Detailed information on the methods is provided below.

3. ELISpot Method

3.1. Isolation of peripheral blood mononuclear cells

Peripheral whole blood samples were collected in sodium citrate tubes and processed within 24–48 h after blood withdrawal to isolate peripheral blood mononuclear cells (PBMC). Whole blood samples were diluted in a ratio of 3:1 with phosphate buffer saline (PBS; Biochrom GmbH, Berlin, Germany) to avoid clotting and then isolated by Ficoll density gradient centrifugation (GE Healthcare Bio-Sciences AB, Uppsala, Sweden). Samples were centrifuged at a rate of 1000 $\times$ g for 30 min at room temperature with brake off. The PBMC layer was collected and washed three times (twice with PBS and once with AIM-V (Thermo Fisher Scientific Inc., Waltham, United States)). Finally, cells were counted and adjusted to 2 $\times$ 10^6 cells/ml for use in ELISpot assay. The technicians were blinded to the clinical data.

3.2. ELISpot assay

The AID/GenID CoV-*i*Spot IFN-γ + IL-2 (ELSP7010; AID GmbH, Strassberg, Germany) detection kit was used for the ELISpot experiments conducted in this study. Briefly, 96-well membrane plates were coated with capture antibodies against human IFN-γ and human IL-2. In each test, complete medium alone and Pokeweed mitogen were used as negative and positive controls, respectively. Furthermore, anti-CD28 was added to each well for co-stimulation.

For all samples, each control and antigen stimulation was performed in duplicates with 2 $\times$ 10^5 PBMC/well. For stimulation, plates were incubated at 37 °C and 5% CO_2 for 16–20 hr. After washing steps, the different cytokine fluorospots were detected followed by the addition of fluorescent labelled antibody conjugates which were incubated for one hour. The next day, the spots obtained were automatically counted with the Fluorspot Reader version 8 (AID GmbH, Strassberg, Germany). Fig. 1A and B show representative FluoroSpot wells for each cytokine-producing T cell against antigen S. Any antigen-specific ELISpot test with less than 5 spots/2 $\times$ 10^5 PBMC was considered as negative when assessed in a qualitative manner. The results were considered after subtracting to each well the responses obtained in the respective negative control wells.

The AID/GenID CoV-*i*Spot detection kit includes one SARS-CoV-2 specific peptide pool (SARS-CoV-2 Peptide-Mix) that allows maximal differences to corona viruses other than SARS-CoV-2 (e.g., SARS-CoV-2, SARS-CoV, middle east respiratory syndrome-coronavirus, other corona viruses causing the common cold) and an additional peptide pool with a maximum consensus across different types of the coronaviridae family (PAN–Corona Peptide-Mix).

The majority of the SARS-CoV-2 specific peptides included in the AID/GenID SARS-CoV-2 Peptide-Mix are located in the N-terminal region of the spike protein while the conserved regions included in the PAN–Corona Peptide-Mix represent the C-terminal region. It should be noted that the used antigen peptide pools are not affected by the current key mutations 69–70 del, E484K, N501Y, and D614G.

Representative example results of 12 (columns 1–12) dialysis patients after vaccination, analysed with the AID/GenID CoV-*i*Spot FluoroSpot Assay. Panel A shows the secretion of interferon-γ (green channel) and panel B shows the secretion of interleukin-2 (orange channel). Rows A–B represent the negative control, C–D represent the positive control, E–F represent the stimulation with the SARS-CoV-2 specific Peptide-Mix (SARS-CoV-2), and G–H represent the stimulation with the Coronaviridae family specific PAN–Corona Peptide-Mix (PAN–Corona).

SARS-CoV-2, severe acute coronavirus type-2.

3.3. SARS-CoV-2-specific antibodies

SARS-CoV-2-specific antibodies were quantified using plasma from citrated whole blood samples using an immunoglobulin G (IgG) assay coated with a recombinant receptor-binding domain

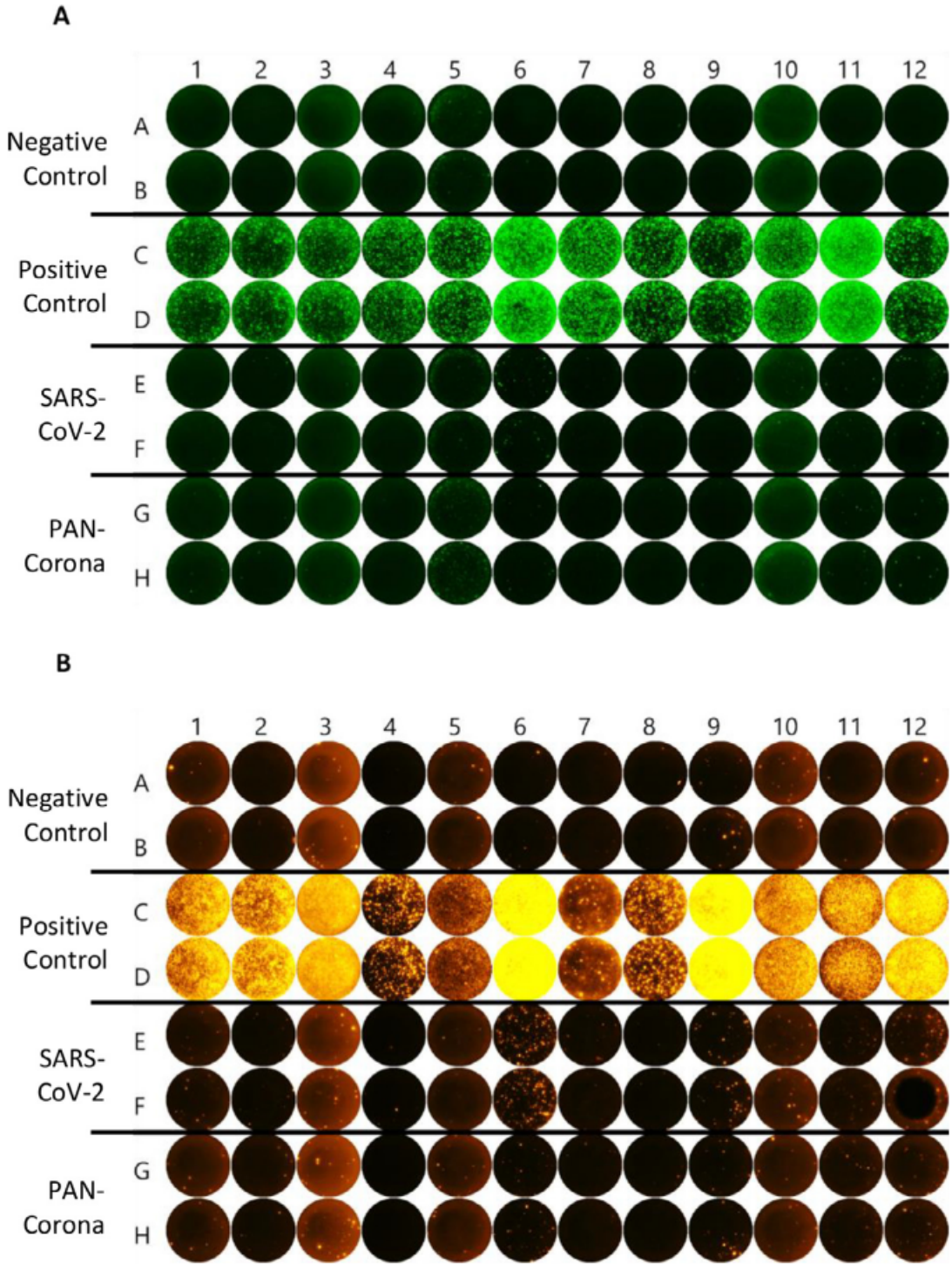

Fig. 1. SARS-CoV-2-specific T-cell responses using a multicolor FluoroSpot Immune assay.

of the SARS-CoV-2 spike protein antigen using an the in-house dot plot array provided by GenID. Antibody levels are expressed in% intensity of gray scale, ranging from 0 to 100 percent black, with an intensity of $>16\%$ considered positive and $\leq 16\%$ considered negative, respectively. Furthermore, SARS-CoV-2-specific antibodies from serum samples against the spike protein and nucleocapsid protein were performed by the Institute of Medical Virology (Giessen, Germany) using antibody chemiluminescent microparticle immunoassay (Anti-S AdviseDx SARS-CoV-2 IgG II and Anti-N Abbott Architect SARS-CoV-2 IgG, Abbott, Chicago, IL, USA). Anti-S levels after infection or vaccination were expressed as AU(arbitrary unit)/ml.

Ethics Statements

The research was carried out in accordance in accordance with the Declaration of Helsinki. The project was approved by the local Ethical committee (AZ 126/21). Written informed consent was obtained from all participants prior to enrollment in the study.

CRediT Author Statement

Hristos Karakizlis: Conceptualization, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration; **Christian Nahrgang:** Conceptualization, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project administration; **Kevin Strecker:** Conceptualization, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration; **Jiangping Chen:** Investigation, Writing - Review & Editing, Project administration; **Mostafa Aly:** Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration; **Heiko Slanina:** Conceptualization, Investigation, Resources, Writing - Review & Editing, Project administration; **Christian G. Schüttler:** Conceptualization, Investigation, Resources, Writing - Review & Editing; **Isla Esso:** Investigation, Writing - Review & Editing, Project administration; **Martin Wolter:** Investigation, Writing - Review & Editing, Project administration; **Darina Todorova:** Investigation, Writing - Review & Editing, Project administration; **Sönke Jessen:** Investigation, Resources, Writing - Review & Editing, Project administration; **Andrea Adamik:** Investigation, Writing - Review & Editing, Project administration; **Claudio Ronco:** Investigation, Writing - Review & Editing, Project administration; **Werner Seeger:** Investigation, Resources, Writing - Review & Editing, Project administration; **Rolf Weimer:** Investigation, Writing - Review & Editing, Project administration; **Martina Sester:** Conceptualization, Investigation, Resources, Writing - Review & Editing, Supervision, Project administration; **Horst-Walter Birk:** Conceptualization, Investigation, Resources, Writing - Review & Editing, Supervision, Project administration; **Faeq Husain-Syed:** Conceptualization, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kevin Strecker is employee of AID/GenID, the manufacturer of the ELISpot assay. None of the other authors declare any competing interests.

Data Availability

Data on immunogenicity and reactogenicity to COVID-19 vaccination among patients receiving maintenance dialysis (Original data) (Mendeley Data).

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4.6. IMMUNOGENICITY AND REACTOGENICITY OF HOMOLOGOUS MRNA-BASED AND VECTOR-BASED SARS-COV-2 VACCINE REGIMENS IN PATIENTS RECEIVING MAINTENANCE DIALYSIS (A6)

***Hristos Karakizlis**, Christian Nahrgang, Kevin Strecker, Jiangping Chen, Mostafa Aly, Heiko Slanina, Christian G-Schüttler, Isla Esso, Martin Wolter, Darina Todorova, Sönke Jessen, Andrea Adamik, Claudio Ronco, Werner Seeger, Rolf Weimer, Martina Sester, Horst-Walter Birk, Faeq Husain-Syed*

Dialysepatienten sind anfällig für COVID-19-bedingte Morbidität und Mortalität. Derzeit gibt es nur wenige Daten zur SARS-CoV-2-spezifischen zellulären und humoralen Immunität nach der Impfung in dieser Bevölkerungsgruppe.

Wir haben eine prospektive monozentrische Studie durchgeführt, in der die spezifischen zellulären (Interferon-γ- und Interleukin-2-ELISpot-Assays) und humoralen Immunantworten (Dot-Plot-Array und Chemilumineszenz-Mikropartikel-Immunoassay [CMIA]) 4 und 6 Wochen nach einer Einzeldosis oder einer vollständigen homologen Zweifachdosis-SARS-CoV-2-Impfung bei 60 Dialysepatienten (6 davon mit einer Vorgeschichte von COVID-19) untersucht wurden.

Unsere Ergebnisse haben gezeigt, dass Dialysepatienten eine hohe Serokonversionsrate (91,7 %) aufweisen, die Anti-Spike-IgG-Antikörper (CMIA) jedoch nach der vollständigen Immunisierung schnell abnehmen. Nur 51,7 % der Patienten entwickelten eine T-Zell-Immunantwort. Eine hohe Anzahl an Anti-Spike-IgG-Antikörpern kann eine bessere zelluläre Immunität vorhersagen. Während Patienten mit einer früheren COVID-19-Impfung die beste Reaktion nach einer Impfung zeigten, könnten SARS-CoV-2-naive Patienten von einer dritten Impfung profitieren.

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Immunogenicity and reactogenicity of homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimens in patients receiving maintenance dialysis

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ABSTRACT

Patients receiving maintenance dialysis (MD) are vulnerable to COVID-19-related morbidity and mortality. Currently, data on SARS-CoV-2-specific cellular and humoral immunity post-vaccination in this population are scarce.

We conducted a prospective single-center study exploring the specific cellular (interferon-γ and interleukin-2 ELISpot assays) and humoral immune responses (dot plot array and chemiluminescent microparticle immunoassay [CMIA]) at 4 weeks and 6 weeks following a single dose or a complete homologous dual dose SARS-CoV-2 vaccine regimen in 60 MD patients (six with a history of COVID-19).

Our results show that MD patients exhibit a high seroconversion rate (91.7%) but the anti-spike IgG antibodies (CMIA) tend to wane rapidly after full immunization. Only 51.7% of the patients developed T cell immune response. High anti-spike IgG antibodies may predict a better cellular immunity. While patients with prior COVID-19 showed the best response after one, SARS-CoV-2-naïve patients may benefit from a third vaccine injection.

1. Introduction

Compared with the general population, patients receiving maintenance dialysis (MD) are at increased risk for morbidity and mortality associated with coronavirus disease 2019 (COVID-19) [1]. The poor outcomes have been attributed to their higher comorbidity burden as well as their increased age, immunologically deficient state from kidney failure, or immunosuppressive medications [2–4]. Compounding these factors, patients undergoing in-center dialysis cannot self-isolate, as they are required to attend their dialysis treatments thrice weekly at a dialysis center, to which they are often transported by a ride-sharing vehicle.

Currently, the European Medicines Agency (EMA) has approved two

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mRNA-based COVID-19 vaccines (mRNA-1273 [Moderna Biotech] and BNT162b2 [Pfizer–BioNTech]) and two vector-based vaccines (ChAdOx1 nCoV-19 [Oxford–AstraZeneca]; Ad26.COV2·S [Johnson & Johnson–Janssen]) [5]. These vaccines induce robust humoral and cellular immune responses against the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) spike protein in healthy individuals, which, protect from the risk of subsequent infection [6,7]. However, whether the results are generalizable to patients with kidney failure is unknown, as the effectiveness of the vaccines has not been explicitly tested in this population due to their common exclusion from SARS-CoV-2 vaccination trials [8,9]. So far, the limited data available suggest a diminished vaccine response in MD patients [10,11]. Therefore, there is an urgent need for more data to allow adaptation of the vaccination protocols to achieve adequate antiviral protection for this vulnerable population, if needed.

The main objective of the present study was to examine the humoral and cellular immunogenicity and reactogenicity of a homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimen in patients receiving MD.

2. Materials and methods

2.1. Study design and participants

This prospective, single-center cohort study included patients aged ≥18 years receiving thrice-weekly in-center dialysis (hemodialysis or peritoneal dialysis) at the Patienten-Heimversorgung outpatient dialysis center at University Hospital Giessen and Marburg, Giessen, Germany. At the time of enrollment, the dialysis center served 84 hemodialysis patients and 5 peritoneal dialysis patients. Patients were enrolled if they had: i) received a homologous mRNA-based or a single-dose or homologous dual dose vector-based vaccine regimen (with or without history of COVID-19), and ii) no laboratory evidence of current SARS-CoV-2 infection. The interval between the first and second injections was determined as per EMA guidelines [5]: 3–4 weeks for homologous mRNA-based vaccines and 4–12 weeks for the vector-based single dose (Ad26.COV2·S) or homologous vector-based ChAdOx1 nCoV-19 vaccine. All blood samples were obtained prior to dialysis treatment at 4 weeks (T1) and 6 weeks (T2) after complete vaccination, with a tolerance range of ±2 days. Local and systemic adverse events after the first and second dose were self-reported using a standardized questionnaire.

The study was approved by the local human research ethics committee (AZ 126/21) and complied with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study.

2.2. Procedures and measurements

2.2.1. Stimulation assays

Vaccine-induced SARS-CoV-2-specific T cells were quantified from citrated whole blood using a multicolor FluoroSpot Immune assay kit (CoV-iSpot, FluoroSpot Assay, AID/GenID, Straßberg, Germany) that detects functional T cells and an interferon (IFN)-γ and interleukin (IL)-2 reaction specifically against SARS-CoV-2. The results were evaluated by calculating the ratio of the antigen specific reaction and negative control (NC) (stimulation index, SI). Any antigen-specific FluoroSpot test with an SI of ≤2 (NC > 2) or ≤ 5 (NC < 2), depending on the background stimulation, was considered negative when assessed quantitatively. For NC <2 a stimulation index of >5 – < 7 was considered borderline and a SI ≥ 7 was considered positive, whereas for NC ≥2 a stimulation index of >2 – ≤ 3 was considered borderline and a SI > 3 was considered positive. A reactive response was considered when at least one timepoint showed a reactive pattern and the other timepoint was reactive or borderline or negative or invalid. A borderline response was considered when one timepoint was borderline and the other timepoint was borderline or negative or invalid. A negative response was considered when one timepoint was negative and the other timepoint was negative or invalid. Only when both timepoints were invalid the response was considered as invalid. GenID performed all FluoroSpot tests, blinded to the clinical data. The Supplementary Material provides a detailed description of the ELISpot method.

2.2.2. Analysis of SARS-CoV-2-specific antibodies

SARS-CoV-2-specific antibodies were quantified using plasma from citrated whole blood samples using an immunoglobulin G (IgG) assay coated with a recombinant receptor-binding domain of the SARS-CoV-2 spike protein antigen using an in-house dot plot array by GenID, blinded to the clinical data. Antibody levels are expressed in % intensity of gray scale, ranging from 0 to 100% black, with an intensity of >16% considered positive and ≤ 16% considered negative, respectively. In addition, SARS-CoV-2-specific antibodies from serum samples against the spike protein and nucleocapsid protein were performed by the Institute of Medical Virology (Giessen, Germany) using antibody chemiluminescent microparticle immunoassay (CMIA; Anti-S AdviseDx SARS-CoV-2 IgG II and Anti-N Abbott Architect SARS-CoV-2 IgG, Abbott, Chicago, IL, USA). The anti-N array (measured in S/CO) was used to detect a previous infection. Anti-S levels after infection or vaccination were expressed as AU (arbitrary unit)/mL with levels >50 AU/mL defined as positive and ≤ 50 AU/mL as negative.

2.2.3. Other laboratory methods

All other blood samples were analyzed at the local Institute of Laboratory Medicine at University Hospital Giessen and Marburg, Giessen, where they were processed within 30 min of collection and centrifuged for 10 min at 3000 ×*g*. Serum creatinine was measured by a photometric-enzymatic method on an ADVIA Chemistry XPT analyzer (enzymatic creatinine; Siemens Healthineers, Erlangen, Germany), with calibration to reference measurements for isotope dilution mass spectrometry. Ferritin was measured by chemiluminescent immunoassay (CLIA) on a Centaur XPT analyzer (Siemens Healthineers). Soluble IL-2 receptor and IL-6 were determined on a Siemens Immulite 1000 system with Siemens reagents.

2.2.4. Other measures

The other variables included kidney failure etiology, dialysis vintage and dose (Kt/V for thrice-weekly hemodialysis [12] and weekly Kt/V for peritoneal dialysis [13]), previous SARS-CoV-2 infection, and use of immunosuppressive therapy.

2.3. Statistical analysis

Descriptive statistics are expressed as the median [interquartile range] for numeric variables and as n (%) for categorical variables. Differences between two independent groups were tested with the Mann-Whitney test or independent *t*-test according to the variables' distribution normality. Categorical variables were tested with the chi-square test or Fisher's exact test. Paired ordinal data were compared using the Wilcoxon signed-rank test; paired nominal data were compared using the McNemar test. Univariate and multivariate logistic regression analyses with backwards elimination were conducted with IL-2 or IFN-γ ELISpot test reactivity at either T1 or T2 as a dependent variable. Independent variables with significant associations in the univariate analysis ($p < 0.1$) were further included in the multivariate regression analysis. The statistical analysis was performed with SPSS Statistics 26 (IBM, Ehningen, Germany). P-values <0.05 were considered significant.

3. Results

3.1. Participants

A total of 60 patients were enrolled in this study. All patients had

Table 1
Demographic and clinical characteristics of the cohort.

	Total (n = 60)	mRNA-based vaccines (mRNA-1273/ BNT162b2) (n = 51)	Vector-based vaccines (ChAdOx1 nCoV-19Ad26. COV2-S) (n = 9)	p-value
Demographics				
Age, years	65.4 [54–75]	66 [51–75]	64 [58–73]	0.99
Male sex, n (%)	38 [63.3%]	33 [64.7%]	5 [55.6%]	0.71
Dry weight, kg	76 [64–89.5]	75 [64–89]	84 [54–92]	0.81
Body mass index, kg/m^2	26.1 [22–29]	26.0 [22–28]	27.6 [20−1]	0.88
Comorbidities				
Hypertension, n (%)	54 (90%)	46 (90.2%)	8 (88.9%)	1.0
Diabetes mellitus, n (%)	21 (35%)	18 (35.3%)	3 (33.3%)	1.0
Coronary artery disease, n (%)	30 (50%)	25 (49%)	5 (55.6%)	1.0
History of stroke, n (%)	7 (11.7%)	5 (9.8%)	2 (22.2%)	0.28
Immunosuppressive therapy, n (%)	7 (12.5%)	5 (9.8%)	2 (22.2%)	0.28
Cause of kidney failure, n (%)				0.91
Nephrosclerosis	10 (16.7%)	9 (17.6%)	1 (11.1%)	
Diabetic nephropathy/ nephrosclerosis	12 (20%)	10 (19.6%)	2 (22.2%)	
Cardiorenal syndrome	10 (16.7%)	9 (17.6%)	1 (11.1%)	
Glomerulonephritis	13 (21.7%)	10 (19.6%)	3 (33.3%)	
Interstitial nephritis	3 (5%)	3 (5.9%)	–	
ADPKD	4 (6.7%)	4 (7.8%)	–	
Cancer	5 (8.3%)	4 (7.8%)	1 (11.1%)	
Unknown	3 (5%)	2 (3.9%)	1 (11.1%)	
Dialysis data				
Dialysis modality, n (%)				
Hemodialysis	53 (88.3%)	44 (86.3%)	9 (100%)	0.58
Peritoneal dialysis	7 (11.7%)	7 (13.7%)	–	N/A
Dialysis vintage, months	32.5 [15–49]	35.0 [15.0–50.0]	26.0 [6.5–34.0]	0.16
Kt/V	1.6 [1.4–1.7]	1.6 [1.4–1.7]	1.4 [1.3–1.6]	0.11
Hemodialysis	1.6 [1.4–1.7]	1.6 [1.4–1.7]	1.4 [1.3–1.6]	
Peritoneal dialysis	2.4 [1.6–3.5]	2.4 [1.7–2.9]	–	
Baseline clinical data				
Leucocyte count, g/L	6.8 [4.8–8.3]	7.0 [5.2–8.4]	5.0 [4.4–7.3]	0.34
Differential count, g/L				
Total neutrophils	4.4 [2.9–6.3]	4.7 [2.8–6.5]	3.6 [2.9–5.2]	0.46
Total lymphocytes	1.2 [0.8–1.5]	1.2 [0.9–1.5]	1.1 [0.7–1.4]	0.62
Total basophils	0.03 [0.02–0.04]	0.02 [0.01–0.04]	0.03 [0.02–0.03]	0.87
Total monocytes	0.6 [0.5–0.8]	0.6 [0.5–0.8]	0.6 [0.4–0.7]	0.70
Total eosinophils	0.2 [0.1–0.3]	0.2 [0.1–0.3]	0.3 [0.1–0.4]	0.48
Hemoglobin, g/dL	10.8 [10.3–11.4]	10.9 [10.4–11.4]	10.5 [9.8–11.8]	0.44
Serum creatinine, mg/dL[a]	7.0 [5.2–8.7]	6.9 [5.5–8.9]	7.6 [4.4–8.6]	1.0
Urea, mg/dL[b]	120 [97–135]	120 [110–136]	85 [79–134]	0.32
Phosphate, mmol/L	1.7 [1.4–1.9]	1.8 [1.4–1.9]	1.4 [1.3–1.9]	0.44
Parathyroid hormone, pg/mL	299 [207–400]	315 [214–413]	280 [80–314]	0.19
Albumin, g/dL	40.4 [38.2–42.5]	40.1 [38.0–42.2]	42.3 [40.9–42.7]	0.12
C-reactive protein, mg/L	9.8 [2.2–20.2]	10.2 [2.3–20.0]	2.7 [0.8–25.0]	0.74
Total IgG, g/L	10.8 [7.3–14.0]	10.5 [7.3–14.0]	10.9 [6.8–14.0]	0.94
IL-6, μg/L	10.0 [10.0–11.5]	10.0 [10.0–11.5]	10.0 [10.0–13.6]	1.0
Soluble IL-2 receptor, U/mL	1284 [873–1864]	1284 [873–1927]	1571 [1001–1844]	0.71
Ferritin, μg/L	228 [82–542]	214 [76–479]	523 [108–916]	0.17

Values are the median [interquartile range], or n (%).
ADPKD, autosomal dominant polycystic kidney disease; IgG, immunoglobulin G; IL-2, interleukin-2; IL-6, interleukin-6.
[a] To convert the values for serum creatinine to μmol/L, multiply by 88.4.
[b] To convert the values for urea to blood urea nitrogen, multiply by 0.467.

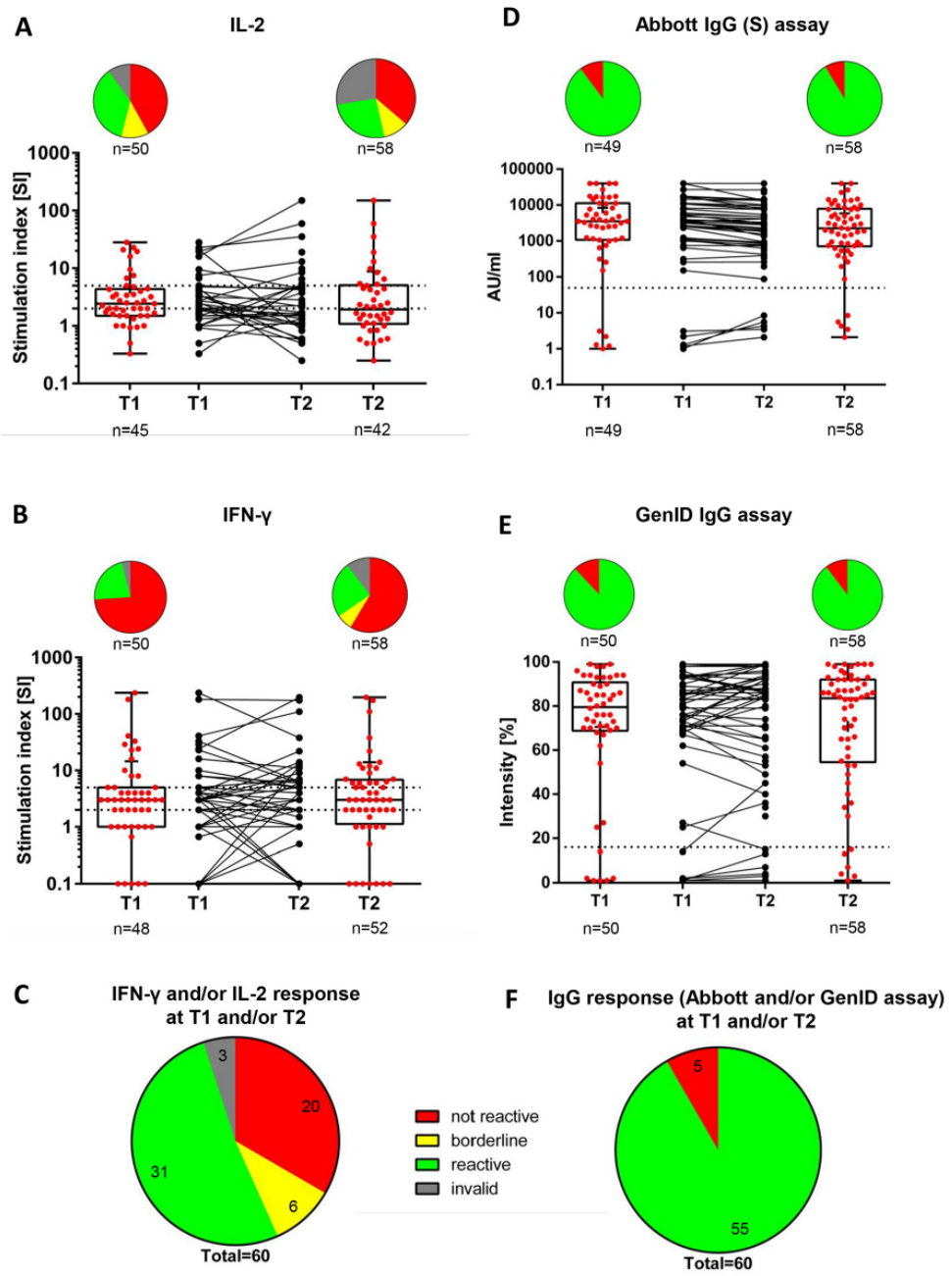
either received a single dose or a dual-dose homologous vaccine regimen. Fifty-one patients had received mRNA-based vaccines (BNT162b2, n = 49; mRNA-1273, n = 2); nine patients had received vector-based vaccines (ChAdOx1 nCoV-19, n = 6; Ad26.COV2·S, n = 3). Six patients had received a booster vaccination 6 months after SARS-CoV-2 infection. Table 1 shows the characteristics of the study population; the median age of the population was 65.4 years; 63.3% were male; 35% had diabetes mellitus; 90% had hypertension, and 50% had coronary heart disease. The main causes of kidney failure were glomerulonephritis (21.7%), diabetes (20%), and nephrosclerosis (16.7%). No demographic differences in the demographic data were observed between patients receiving mRNA-based vaccines vs. vector-based vaccines. The median length of time on dialysis was 33 [15–49] months. Hemodialysis was the dialysis modality adopted by 88.3% of the study population. No difference was observed in key laboratory parameters between T1 and T2 (Supplementary Material Table S1). A total of 50 and 58 patient samples were analyzed at T1 and T2, respectively.

3.2. IL-2 and IFN-γ stimulation assays

We first analyzed all patient samples irrespective of the vaccine type and history of COVID-19. The majority of patients showed no reactivity in the IL-2 and IFN-γ ELISpot assays at T1 (42.0% and 74.0%, respectively) and T2 (36.2% and 58.6%, respectively), while there was a reactive pattern in the IL-2 and IFN-γ ELISpot assays at T1 in 36.0% and 22.0% of the patients, respectively, and at T2 in 25.9% and 24.1% of the patients, respectively (Fig. 1A and B). An IL-2 and/or IFN-γ reactivity in at least one time point was observed in 51.7% of patients (Fig. 1C), whereas a non-response in all samples was observed in 33.3% of the patients. Borderline reactivities and invalid test results were observed in 10.0% and 5.0% of patients, respectively (Fig. 1A). There was no difference in the median IL-2 and IFN-γ reactivities between both time points (p = 0.93 and p = 0.85, respectively; Table 2).

3.3. Analysis of SARS-CoV-2-specific antibodies

In the Abbott array, 89.8% of patients had SARS-CoV-2 anti-spike IgG antibodies above the detection limit (IgG >50 AU/mL at T1 and remained positive at T2, whereas 8.6% of patients were classified as negative (IgG ≤ 50 AU/mL) at both time points (Fig. 1E). However, the median SARS-CoV-2 anti-spike IgG antibody levels were significantly lower at T2 compared to T1 (2240 [756–7687] AU/mL vs. 3517



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[1070–11,164] AU/mL; $p < 0.001$; Table 2). In contrast, when using the GenID assay, the median percentage of median SARS-CoV-2 anti-spike IgG antibodies were not significantly different between T2 and T1 (84.5% [58%–92.7%] vs. 79.5% [68.5%–92.2%]; $p = 0.371$; Table 2). The GenID IgG assay showed that 55 of 60 patients (91.7%) were positive (IgG intensity >16%) in at least one timepoint, while five patients (8.3%) were negative at both T1 and T2 (IgG intensity ≤16%) (Fig. 1E).

Except for one case, both the Abbott and GenID assays yielded the same results when classifying the humoral response as either positive or negative (Supplementary Material Fig. S1). A positive test result in at least one assay at either T1 or T2 was observed in 91.7% of patients, whereas 8.3% were consistently negative in both assays (Fig. 1D).

Overall, five patients (8.3%) did not generate anti-spike IgG antibodies. Four of these patients showed no cellular immune response and

Fig. 1. Vaccine-induced SARS-CoV-2-specific IL-2 (A) and IFN-γ (B) and IL-2 and/or IFN-γ (C)-producing T cells and SARS-CoV-2 anti-spike IgG antibodies as determined using the Abbott assay (D), GenID assay (E), and both (F) at T1 and T2.
A) T1 ($n = 50$): Not reactive, 21 (42.0%); borderline, 6 (12.0%); reactive, 18 (36.0%); invalid, 5 (10.0%). T2 ($n = 58$): Not reactive, 21 (36.2%); borderline, 6 (10.3%); reactive, 15 (25.9%); invalid, 16 (27.6%). T1 vs. T2 ($p = 0.73$).
B) T1 ($n = 50$): Not reactive, 37 (74.0%); borderline, 0 (0.0%); reactive, 11 (22.0%); invalid, 2 (4.0%). T2 ($n = 58$): Not reactive, 34 (58.6%); borderline, 4 (6.9%); reactive, 14 (24.1%); invalid, 6 (10.3%). T1 vs. T2 ($p = 0.12$).
C) T1 and/or T2 ($n = 60$): Not reactive, 20 (33.3%); borderline, 6 (10.0%); reactive, 31 (51.7%); invalid, 3 (5.0%).
D) T1 ($n = 50$): Positive, 44 (88.0%)[a]; negative, 6 (12.0%)[b]. T2 ($n = 58$): Positive, 52 (89.7%)[a]; negative, 6 (10.3%)[b]. T1 vs. T2 ($p = 1.0$)[e].
E) T1 ($n = 49$): Positive, 44 (89.8%)[c]; negative, 5 (10.2%)[d]. T2 ($n = 58$): Positive, 53 (91.4%)[c]; negative, 5 (8.6%)[d]. T1 vs. T2 (p = NS)[e].
F) T1 and/or T2 ($n = 60$): Positive, 55 (91.7%); negative, 5 (8.3%).
The dashed horizontal lines indicate the cut-off for positivity (reactive); the area between the horizontal lines indicates the borderline zone used in each GenID assay.
[a]Positive refers to antibody levels >16%.
[b]Negative refers to antibody levels ≤16%.
[c]Positive refers to antibody concentration > 50 AU/mL.
[d]Negative refers to antibody concentration ≤ 50 AU/mL.
[e]McNemar's test for paired nominal data was used.
IFN-γ, interferon-γ; IL-2, interleukin-2; SARS-CoV-2, NS, not significant; severe acute respiratory syndrome-coronavirus type-2; T1, timepoint 1; T2, timepoint 2.

Table 2
Cellular and humoral immune responses following SARS-CoV-2 vaccination at T1 and T2.

	Vaccines (mRNA- and vector-based)		p-value
	T1	T2	
IL-2, SI	2.4 [1.5–4.5] ($n = 33$)	1.6 [1.0–4.7] ($n = 33$)	0.93
IFN-γ, SI	3 [1–5] ($n = 43$)	3 [1–7] ($n = 43$)	0.85
SARS-CoV-2 anti-spike IgG, AU/mL (Abbott array)	3517 [1070–11,164] ($n = 48$)	2240 [756–7687] ($n = 48$)	**<0.001**
SARS-CoV-2 anti-spike IgG, % (GenID assay)	79.5 [68.5–92.2] ($n = 48$)	84.5 [58–92.7] ($n = 48$)	0.37

Values are the median [interquartile range]. Bolded p-values denote statistical significance at the $p < 0.05$ level. We conducted analyses of patients who had valid measurements at both time points.
IFN-γ, interferon-γ; IgG, immunoglobulin G; IL-2, interleukin-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; T1, timepoint 1; T2, timepoint 2.

one patient showed a positive cellular immune response at time T1 but a negative one at time T2 (Table S2 in the Supplementary Material). Four patients were on immunosuppressive therapy (two patients received rituximab and prednisolone due to MPO-ANCA (myeloperoxidase–anti-neutrophil cytoplasmic antibody)-positive vasculitis, one patient was a pancreatic islet transplant recipient, one patient received anti-myeloma chemotherapy), while the fifth patient had a history of Hodgkin lymphoma. Notably, the remaining 2 patients who were on immunosuppressive therapy did develop anti-spike IgG antibodies (one patient received full vaccination approximately 1 month prior to the initiation of immunosuppressive therapy due to first diagnosis of MPO-ANCA positive vasculitis with renal involvement, one patient had tacrolimus monotherapy after kidney allograft failure).

3.4. Association between humoral and cellular immune response following vaccination

Patients showing IL-2 producing T cells had higher levels of SARS-CoV-2 anti-spike IgG at both timepoints in both the Abbott array (T1, $p = 0.024$; T2, $p = 0.001$) and the GenID assay (T1, $p = 0.024$; T2, $p = 0.007$) compared to those who did not show any IL-2 reactivity. We excluded patients with borderline results from the comparison. Likewise, we found higher levels of SARS-CoV-2 anti-spike IgG at both timepoints in both the Abbott array (T1, $p = 0.002$; T2, $p > 0.001$) and GenID assay (T1, $p = 0.019$; T2, $p = 0.01$) in patients with IFN-γ ELISpot positive reactivity compared to the non-reactive patients.

Multivariate logistic regression analysis showed that among the variables included, the ELISpot assay reactivity regarding IL-2 (T1: odds ratio [OR] = 2.40 (95% confidence interval [CI]: 1.10–5.40), $p = 0.028$; T2: OR = 6.85 [95% CI: 1.49–31.50], $p = 0.014$) and IFN-γ (T1: OR = 4.18 [95% CI: 1.62–10.80], $p = 0.003$; T2: OR = 9.45 [95% CI: 2.05–43.60], $p = 0.004$) was independently associated with SARS-CoV-2 IgG levels as measured with the Abbott array at both timepoints. We did not find other confounders that had an effect on ELISpot reactivity (Table 3).

3.5. Comparison of cellular and humoral responses between SARS-CoV-2-naïve patients and those with previous COVID-19 and between vaccine regimens

The Abbott assay showed that patients with previous SARS-CoV-2 infection who had received a booster vaccination exhibited higher SARS-CoV-2 anti-spike IgG concentrations at both timepoints when compared to SARS-CoV-2-naïve patients with full vaccination (T1 and T2, $p < 0.001$; Table 4 and Fig. 2). Also, patients with previous SARS-CoV-2 infection showed a higher SI in the IL-2 ELISpot at T1 ($p = 0.004$) but not at T2 ($p = 0.07$). Such patients also had a higher SI in the IFN-γ ELISpot at both timepoints (T1 and T2, $p < 0.001$). Patients with history of COVID had significantly higher levels of response in the GenID assay (91.5% vs. 76%, $p = 0.04$) at time T1, but not at time T2 (92% vs. 83%, $p = 0.15$) (Table 4). The vaccination regimen in the infection-naïve patients did not affect the vaccination response compared to the group with history of COVID-19 (Table S3 and S4 in the Supplementary Material). Also, the dialysis regime (hemodialysis vs. peritoneal dialysis) had no effect on the immunity response (data not shown). However, it should be noted that there was only a small number of patients receiving a vector-based vaccination regimen and peritoneal dialysis and, thus, the groups may be underpowered.

3.6. Reactogenicity of SARS-CoV-2 vaccine regimen

Adverse events were reported by 28 (46.7%) and 22 (43.1%) patients after the first and second dose, respectively (Supplementary Material Table S5). The onset of adverse events was mostly reported within 3 days after vaccination (after the first dose, 89.3% of patients; after the second dose, 100% of patients). The main reported adverse events were pain and swelling or redness at the injection site (after the first dose, 31.6%; after the second dose, 27.4%) and tiredness/fatigue (after the first dose, 16.7%; after the second dose, 23.5%). No association was observed between the reported reactogenicity and the immune response (data not shown).

Table 3
Association of demographic and clinical characteristics with positive SARS-CoV-2-specific IL-2 reactivity (A) and IFN-γ reactivity (B) at T1 and T2.

(A)

Variable	T1[a]						T2[b]					
	Univariate association			Multivariate association			Univariate association			Multivariate association		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.982	(0.944–1.02)	0.353				0.967	(0.927–1.008)	0.114			
Diabetes mellitus (yes)[c]	1.25	(0.320–4.8)	0.748				0.733	(0.192–2.806)	0.651			
Dialysis modality (PD)[c]	0.353	(0.033–3.7)	0.387				0	(0–0)	0.999			
Dialysis duration	1	(0.988–1.001)	0.880				1.001	(0.990–1.013)	0.853			
Previous COVID-19 infection (recovered)[c]	7.69	(0.805–73.5)	**0.077**[d]				5	(0.466–53.6)	0.184			
Type of vaccine (vector vaccine)[c]	0.353	(0.33–3.7)	0.387				0.429	(0.040–4.57)	0.483			
SARS-CoV-2 anti-spike antibodies (in 10,000)	2.44	(1.1–5.4)	**0.028**[d]	2.401	(1.102–5.402)	**0.028**	6.848	(1.487–31.5)	**0.014**[d]	6.848	(1.487–31.50)	**0.014**
Immunosuppressive drugs (yes)[c]	0.750	(0.111–5.074)	0.768				0	(0–0)	0.999			
CRP	1.053	(0.983–1.128)	0.140				0.957	(0.890–1030)	0.241			
IL-6	0.931	(0.825–1.050)	0.243				0.905	(0.775–1057)	0.209			
Ferritin	1	(0.999–1.002)	0.807				1	(0.998–1001)	0.615			

(B)

Variable	T1[a]						T2[a]					
	Univariate association			Multivariate association			Univariate association			Multivariate association		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.989	(0.949–1.032)	0.622				0.975	(0.939–1.013)	0.201			
Diabetes mellitus (yes)[b]	1.190	(0.291–4.867)	0.808				0.794	(0.219–2.880)	0.725			
Dialysis modality (PD)[b]	0.640	(0.067–6.142)	0.699				0.446	(0.047–4.210)	0.481			
Dialysis duration	1.004	(0.989–1.018)	0.618				1.004	(0.990–1.018)	0.599			
Previous COVID-19 infection (recovered)[b]	1.195e+10	(0–0)	0.999				5.493e+9	(0–0)	0.999			
Type of vaccine (vector vaccines)[b]	0.640	(0.067–6.142)	0.699				0.577	(0.059–5.674)	0.637			
SARS-CoV-2 anti-spike antibodies (in 10,000)	4.18	(1.6–10.8)	**0.003**[c]	4.18	(1.62–10.80)	**0.003**	9.447	(2.047–43.60)	**0.004**[c]	9.447	(2.047–43.60)	**0.004**
Immunosuppressive drugs (yes)[b]	0.640	(0.067–6.14)	0.699				2.667	(0.337–21.11)	0.353			
CRP	0.997	(0.978–1.016)	0.730				0.973	(0.931–1.016)	0.216			
IL-6	0.952	(0.847–1.069)	0.402				0.948	(0.864–1.040)	0.261			
Ferritin	1	(0.999–1.001)	0.570				1.001	(1–1.003)	**0.090**[c]			

Bolded p-values denote statistical significance at the $p < 0.05$ level.
[a]Thirty-nine cases were included in the logistic regression analysis due to missing cases.
[b]Thirty-six cases were included in the logistic regression analysis due to missing cases.
[c]Refers to indicator.
[d]Refers to variables included in the multivariate logistic regression analysis with backward elimination.
95% CI, 95% confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL-6, interleukin-6; OR, odds ratio; PD, peritoneal dialysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; T1, timepoint 1; T2, timepoint 2.
Bolded p-values denote statistical significance at the $p < 0.05$ level.
[a]Forty-eight cases were included in the logistic regression analysis due to missing cases.
[b]Refers to indicator.
[c]Refers to variables included in the multivariate logistic regression analysis with backward elimination.
95% CI, 95% confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL-6, interleukin-6; OR, odds ratio; PD, peritoneal dialysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; T1, timepoint 1; T2, timepoint 2.

4. Discussion

4.1. Key findings

We prospectively quantified the humoral and cellular immune response at both 4 weeks and 6 weeks after full vaccination in patients receiving MD. Most patients (91.7%) had detectable SARS-CoV-2 anti-spike IgG antibodies in at least one time point. However, the median SARS-CoV-2 anti-spike IgG antibody levels measured with the Abbott assay were significantly lower at 6 weeks post-vaccination compared to 4 weeks, indicating that although a full vaccination regimen was sufficient for inducing SARS-CoV-2-specific antibodies, the antibody levels tended to decrease rapidly. In addition, although only 51.7% of patients were reactive in the SARS-CoV-2-specific T cell activation ELISpot assays, there were no detectable differences in the IL-2 or IFN-γ reactivities between both time points, suggesting the short-term stability of cellular immunity compared to humoral immunity after full vaccination. Finally, patients receiving a booster vaccination after SARS-CoV-2 infection showed both better humoral and cellular immunity compared to SARS-CoV-2-naïve patients with full vaccination, whereas patients with immunosuppressive therapy developed almost no detectable humoral or cellular immunity.

4.2. Comparison with previous studies

The observed high humoral immune response to the SARS-CoV-2 spike protein is similar to a recent vaccine trial involving healthy adults [14]. Some studies on the humoral response in hemodialysis patients have reported similar (>90%) seroconversion results [15–18], which are comparatively higher to that of other studies, where 77%–82% of dialysis patients had positive anti-spike IgG antibody levels [11,19–21]. The observed differences in the seroconversion rate among the selected studies may be in part due to the large variation in the number of dialysis patients on immunosuppressive therapy (0%–12.0%) or with a history of cancer (0%–35.2%), as both are recognized risk factors for a diminished immune response following vaccination [11,19,20].

Comparable longitudinal data analyzing the humoral response

Table 4
Comparison of cellular and humoral responses between SARS-CoV-2-naïve and SARS-CoV-2-infected patients with full vaccination.

	Vaccinated with no history of COVID-19		Vaccinated with history of COVID-19		p-value
	Median [IQR]	n	Median [IQR]	n	
SARS-CoV-2 anti-spike IgG antibodies at T1, AU/mL (Abbott)	3180 [1008–6029]	43	40,000 [17,230–40,000]	6	**<0.001**
SARS-CoV-2 anti-spike IgG antibodies at T2, AU/mL (Abbott)	1894 [583–5268]	53	14,653 [10,584–40,000]	5	**<0.001**
SARS-CoV-2 anti-spike IgG antibodies at T1, % (GenID)	76 [67.2–88.2]	44	91.5 [82.7–95.2]	6	**0.042**
SARS-CoV-2 anti-spike IgG antibodies at T2, % (GenID)	83 [54–91]	53	92 [68.5–97]	5	0.15
IL-2 at T1, SI	2 [1.5–3.5]	39	17.7 [3.1–21.4]	6	**0.004**
IL-2 at T2, SI	1.67 [1–4.4]	37	35.3 [1.5–105]	5	0.07
IFN-γ at T1, SI	3 [1–4]	42	35 [20–195]	6	**<0.001**
IFN-γ at T2, SI	3 [1–6]	47	110 [22–186]	5	**<0.001**

Bolded p-values denote statistical significance at the $p < 0.05$ level.
COVID-19, coronavirus disease 2019; IFN-γ, interferon-γ; IL-2, interleukin-2; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus type-2; T1, timepoint 1; T2, timepoint 2.

dynamics at 4 weeks and 6 weeks post-vaccination in MD patients are not available. However, a study group recently indicated waning humoral response 6 months after SARS-CoV-2 vaccination in patients receiving MD [22]. Whether the antibody loss is caused by the impaired immune system in dialysis patients or by the vaccine platforms, or both, remains unclear. Nevertheless, strategies for prolonging and/or boosting host immunity should be evaluated to protect vulnerable populations against SARS-CoV-2 and its variants. Therefore, a third booster dose after 6 months, which is common recommendation in many countries including Germany should be considered to sustain protective humoral immunity in patients with kidney failure [23].

Emerging evidence suggests the requirement of both antibody-mediated and T cell-mediated immunity for effective protection against SARS-CoV-2 [24]. However, our results indicate that a significant proportion of patients may not develop cellular immunity, although almost all patients developed antibodies. Our results are in line with previous studies involving MD patients describing an impaired cellular immune response after SARS-CoV-2 vaccination, with T cell activation of 31%–78% [11,16,18], which is lower compared to that of the general population (88.2%) [25] but higher compared to that of kidney transplant recipients (5.1%–35.0%) [26,27]. The inadequate cellular response after SARS-CoV-2 vaccination in MD patients is consistent with the impaired response reported after hepatitis B virus vaccination in hemodialysis patients [28]. Notably, however, the findings regarding cellular immune response from such studies must be interpreted carefully, given the different vaccine platforms used.

MD patients receiving a booster vaccination after SARS-CoV-2 infection showed better humoral and cellular immunity compared to SARS-CoV-2-naïve patients with full vaccination. Other studies also suggest that prior seropositivity seems to be protective against SARS-CoV-2 infection in MD patients [19,29]. Forbes et al. reported that hemodialysis patients have a robust and sustained antibody response after confirmed COVID-19 infection, with 71% of the cohort having a positive response, indicating increasing antibody positivity during the 6-month follow-up period [30]. The reason for the stronger humoral and cellular immune response in MD patients after natural COVID-19 infection is unknown, but similar findings were reported for immunocompetent individuals and transplant recipients [11,29,30]. It might be intuitive that the high inflammation level observed in MD patients during COVID-19 may contribute to a stronger antigenic challenge and lymphocyte recruitment, generating stronger cellular and humoral immune responses as compared to vaccine-mediated prime-boost immune response.

Yet, it is unclear whether the higher antibody level correlates with better protection against SARS-CoV-2 infection [31,32]. However, our data show that the higher estimates of SARS-CoV-2 anti-spike IgG at both timepoints are associated with a higher rate of cellular immunity. Therefore, we speculate that these patients also have higher protection against SARS-COV-2 infection.

Vaccination side effects did occur in (up to 46.7%) of cases, but were usually mild (local pain and swelling), and were mostly restricted to the first 3 days after vaccination (in 89.3%), in line with previous reports [16,33].

4.3. Study strengths and limitations

A major strength of our study is that we compared humoral and cellular immunity, which have received little attention in the literature. We also measured cellular immunity including both IL-2 and IFN-γ, which allows assessment of both the early and late cellular immune response [34].

The important limitations of our study include the observational, non-randomized study character, small sample size, and limited number of patients receiving a vector-based vaccine regimen and peritoneal dialysis. Moreover, we did not include healthy controls; therefore, we were unable to compare the humoral and cellular immune response against SARS-CoV-2 vaccines between MD patients and healthy controls.

5. Conclusions

The majority of patients receiving MD develop SARS-CoV-2 anti-spike IgG antibodies after a single dose or homologous dual dose vaccine regimen, but these antibodies tend to wane rapidly by 6 weeks after full immunization. Only approximately 50% of patients develop T cell immunity. High anti-spike IgG antibodies may predict a better cellular immunity. The level of vaccine response was significantly higher in patients who have had a history of COVID-19. Therefore, while patients with prior COVID-19 showed the best response after one dose, SARS-CoV-2-naïve patients may benefit from a third vaccine injection to optimize immunogenicity and sustain protection.

Compliance with ethical standards

Approval by the local ethics committee (Ethikkommission des Fachbereich Medizin, Justus-Liebig-Universität Giessen) was granted before initiating enrolment (AZ 126/21). Written informed consent was obtained from the patients by a member of the research team.

Availability of data and material

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Competing interests

KS is employee of AID/GenID, the manufacturer of the ELISpot assay. None of the other authors declare any competing interests.

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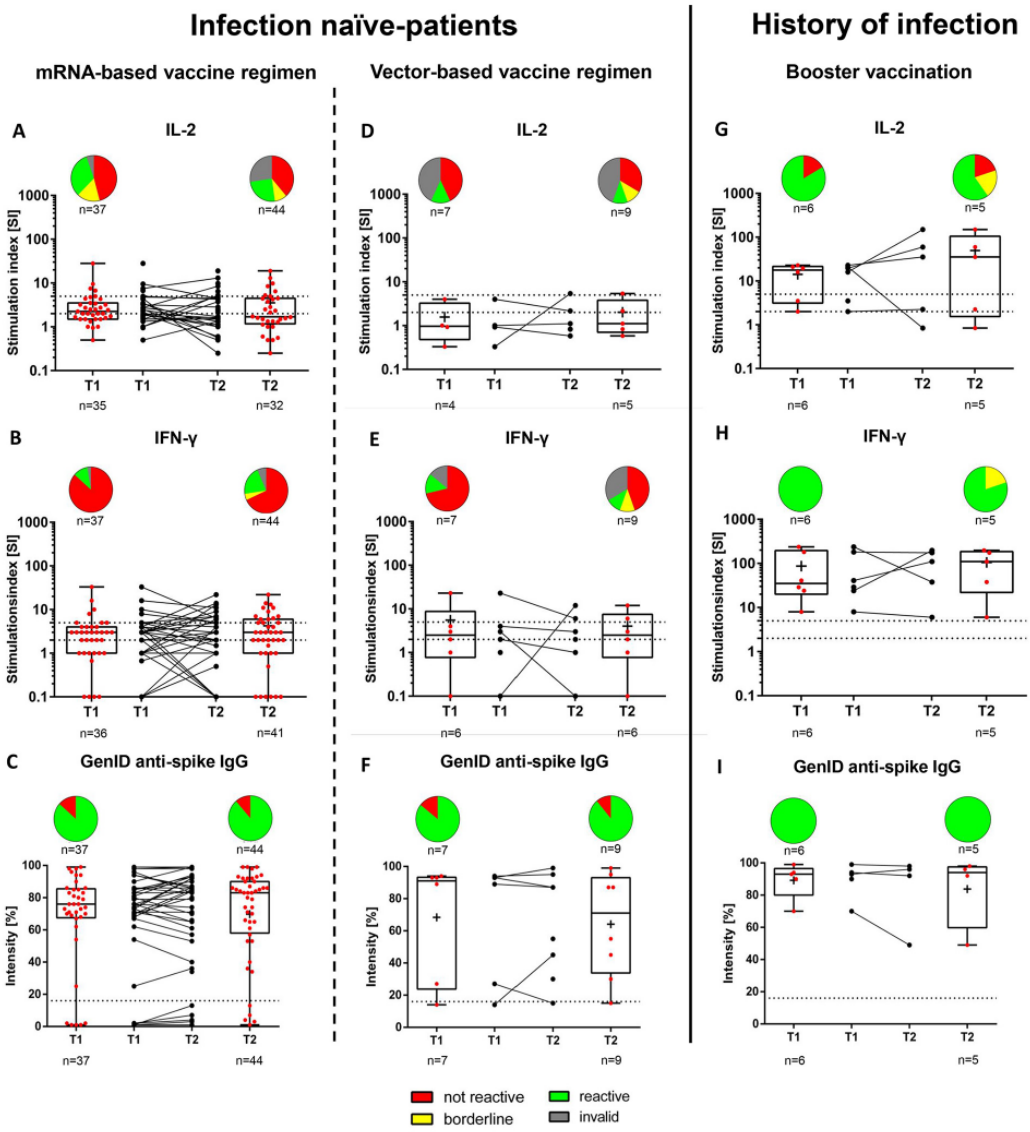

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The authors shared study design, data collection, data analyses, and data interpretation, as well as preparation, review, and approval of the manuscript. The authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format. The corresponding authors had full access to all study data and had final responsibility for the decision to submit for publication.

Fig. 2. Vaccine-induced SARS-CoV-2-specific IL-2- and IFN-γ-producing T cells and SARS-CoV-2 anti-spike IgG antibodies as determined using the GenID assay at T1 and T2, stratified by mRNA vaccine regimen (A–C), vector-based vaccine regimen (D—F), for infection naïve patients, or booster vaccination in patients with a history of SARS-CoV-2 infection (G–I).
A) IL-2: T1 ($n = 37$): Not reactive, 17 (45.9%); borderline, 6 (16.2%); reactive, 12 (32.4%); invalid, 2 (5.4%). T2 ($n = 44$): Not reactive, 17 (38.6%); borderline, 4 (9.1%); reactive, 11 (25.0%); invalid, 12 (27.3%).
B) IFN-γ: T1 ($n = 37$): Not reactive, 32 (86.5%); borderline, 0 (0%); reactive, 4 (10.8%); invalid, 1 (2.7%). T2 ($n = 44$): Not reactive, 30 (68.1%); borderline, 2 (4.5%); reactive, 9 (20.5%); invalid, 3 (6.8%).
C) IgG: T1 ($n = 37$): Positive, 32 (86.5%)[a]; negative, 5 (13.5%)[b]. T2 ($n = 44$): Positive, 39 (88.6%)[a]; negative, 5 (11.4%)[b].
D) IL-2: T1 ($n = 7$): Not reactive, 3 (42.9%); borderline, 0 (0%); reactive, 1 (14.3%); invalid, 3 (42.9%). T2 ($n = 9$): Not reactive, 3 (33.3%); borderline, 1 (11.1%); reactive, 1 (11.1%); invalid, 4 (44.4%).
E) IFN-γ: T1 ($n = 7$): Not reactive, 5 (71.4%); borderline, 0 (0%); reactive, 1 (14.3%); invalid, 1 (14.3%). T2 ($n = 9$): Not reactive, 4 (44.4%); borderline, 1 (11.1%); reactive, 1 (11.1%); invalid, 3 (44.4%).
F) IgG: T1 ($n = 7$): Positive, 6 (85.7%)[a]; negative, 1 (14.3%)[b]. T2 ($n = 9$): Positive, 8 (88.9%)[a]; negative, 1 (11.1%)[b].
G) IL-2: T1 ($n = 6$): Not reactive, 1 (16.7%); borderline, 0 (0%); reactive, 5 (83.3%); invalid, 0 (0%). T2 ($n = 5$): Not reactive, 1 (20.0%); borderline, 1 (20.0%); reactive, 3 (60.0%); invalid, 0 (0%).
H) IFN-γ: T1 ($n = 6$): Not reactive, 0 (0%); borderline, 0 (0%); reactive, 6 (100%); invalid, 0 (0%). T2 ($n = 5$): Not reactive, 0 (0%); borderline, 1 (20.0%); reactive, 4 (80.0%); invalid, 0 (0%).
I) IgG: T1 ($n = 6$): Positive, 6 (100%)[a]; negative, 0 (0%)[b]. T2 ($n = 5$): Positive, 5 (100%)[a]; negative 0 (0%)[b].
All individuals with a history of SARS-CoV-2 infection were vaccinated with one dose of mRNA- BNT162b2 ($n = 6$).
The dashed horizontal lines indicate the cut-off for positivity (reactive); the area between the horizontal lines indicates the borderline zone used in each GenID assay.
[a]Positive refers to antibody levels >16%.
[b]Negative refers to antibody levels ≤16%.
IgG, immunoglobulin G; IFN-γ, interferon-γ; IL-2, interleukin-2.

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Appendix A. Supplementary data

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4.7. HUMORAL AND CELLULAR IMMUNE RESPONSES TO THE MRNA-1273 SARS-COV-2 VACCINE BOOSTER IN PATIENTS ON MAINTENANCE DIALYSIS (A7)

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Dialysepatienten haben ein höheres COVID-19-bezogenes Sterberisiko als die Allgemeinbevölkerung. Hier berichten wir über Follow-up-Daten zu den Immunreaktionen 6 Monate nach dem primären COVID-19-Impfzyklus (T3) und 4 Wochen nach der Auffrischung (T4) durch heterologe und homologe primäre COVID-19-Impfzyklen gegen SARS-CoV-2 bei erwachsenen Patienten, die dreimal wöchentlich eine Zentrumsdialyse erhalten (Hämodialyse) *bzw. mit Peritonealdialyse behandelt werden.*

Wir untersuchten Anti-SARS-CoV-2-Spike-Antikörper mit einem Dot-Plot-Array (GenID, Straßberg, Deutschland) und einem Chemilumineszenz-Mikropartikel-Immunoassay (Anti-S AdviseDx Anti-SARS-CoV-2-Spike-Antikörper II, Abbott, Chicago, IL, USA) sowie T-Zell-Antworten anhand der Sekretion von Interferon(IFN)-γ und Interleukin(IL)-2 aus peripheren Blutleukozyten nach der Stimulation mit SARS-CoV-2-Glykoproteinen (ELISpot-Assay, GenID).

Von der ursprünglichen Kohorte (n = 60) standen 47 Patienten (78,3 %) für eine Nachuntersuchung zur Verfügung (T3: n = 42; T4: n = 46) Alle Patienten erhielten die Booster-Impfung mit dem mRNA-1273-Impfstoff (Moderna Biotech). Die medianen Anti-SARS-CoV-2-Spike-Antikörperspiegel (Abbott-Array) waren bei T3 signifikant niedriger als bei T2 (501 [Interquartilsbereich, 134–1703] vs. 2240 [756–7687] arbiträre Einheiten [AU]/ml; P < 0,001) und stiegen nach dem Booster deutlich auf 40.000 [6855–40.000] AU/ml an (P < 0,001).

Patienten mit einer COVID-19-Vorgeschichte wiesen bei T2 anhaltend höhere Anti-SARS-CoV-2-Spike-Antikörperspiegel auf als Patienten ohne durchgemachte Infektion (Abbott-Array). Patienten mit einer COVID-19-Anamnese hatten auch höhere SARS-CoV-2-spezifische IFN-γ-Spiegel bei T2 (P < 0,001), dies galt aber nicht für IL-2 (P = 0,07). Bei den IFN-γ-SI-Spiegeln bei T3 (P = 0,252) und T4 (P = 0,299) wurden keine Unterschiede zwischen den beiden Gruppen festgestellt.

Unsere Ergebnisse lassen auf eine robuste humorale Immunantwort 6 Monate nach der Grundimmunisierung schließen, diese fiel aber innerhalb von 6 Monaten deutlich ab. Außerdem beobachteten wir eine anhaltend relativ schwache zelluläre Immunantwort nach der Booster-Impfung.

Insgesamt deuten unsere Daten auf eine fortschreitende Abnahme der humoralen Immunität und eine anhaltend relativ schwache zelluläre Immunantwort innerhalb von 6 Monaten hin. Die Auffrischungsimpfung ist jedoch in der Lage, die humorale Immunität wieder deutlich zu erhöhen. Das Auftreten von SARS-CoV-2-Varianten mit hohem Potenzial zur Immunevasion könnte bei Dialysepatienten eine Auffrischungsimpfung 4–6 Monate nach der Booster-Impfung erforderlich machen.

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RESEARCH LETTER

Humoral and cellular immune responses to the mRNA-1273 SARS-CoV-2 vaccine booster in patients on maintenance dialysis

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Maintenance dialysis patients have higher coronavirus disease 2019 (COVID-19)-related mortality risk than the general population [1]. We and others have shown that patients have waning early antibody-mediated and blunted T cell-mediated immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination [1, 2]. Optimizing the vaccination strategy in this population requires an understanding of the humoral and cellular immune response dynamics to SARS-CoV-2 vaccines, but immunogenicity data post-booster after primary COVID-19 vaccine cycle are scarce [3]. Here, we report follow-up data on the immune responses 6 months after primary COVID-19 vaccine cycle (T3) and 4 weeks post-booster (T4) following heterologous and homologous primary COVID-19 vaccine cycle SARS-CoV-2 vaccinations in adult patients receiving thrice weekly, in-center dialysis (hemodialysis and peritoneal dialysis) at the University Hospital Giessen and Marburg, Giessen, Germany [1].

We assessed anti-SARS-CoV-2 spike antibodies using a dot plot array (GenID, Strassberg, Germany) and chemiluminescent microparticle immunoassay (Anti-S AdviseDx anti-SARS-CoV-2 spike antibodies II, Abbott, Chicago, IL, USA), and T-cell responses by interferon (IFN)-γ and interleukin (IL)-2 peripheral blood leukocyte secretion upon SARS-CoV-2 glycoprotein stimulation (ELISpot assay, GenID; Supplementary Methods, Supplementary Table S1: study methods, statistical analysis, patients' characteristics). The local human research ethics committee (AZ 126/21) approved this study and it complied with the Declaration of Helsinki tenets. All participants provided written informed consent before study enrollment.

Of the original cohort ($n = 60$), 47 patients (78.3%) were available for follow-up (T3: $n = 42$; T4: $n = 46$; five

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patients were transferred to other dialysis centers; six patients died from non-COVID-19-associated causes; two patients received boosters outside their dialysis center). Two patients had asymptomatic COVID-19 breakthrough infection despite complete primary COVID-19 vaccine cycle and therefore were only tested at T4 (Supplementary Table S2). The results of the timepoints T1–T2 around the primary COVID-19 vaccine cycle were recently published [1].

All patients received the mRNA-1273 mRNA-based vaccine booster (Moderna Biotech). Figure 1 depicts the humoral and cellular response dynamics 6 weeks (T2), and 6 months (T3) after primary COVID-19 vaccine cycle and 4 weeks (T4) after booster vaccination. The median anti-SARS-CoV-2 spike antibody levels (Abbott array) were significantly lower at T3 than T2 (501 [interquartile range, 134–1703] vs. 2240 [756–7687] arbitrary units [AU]/ml; $P < 0.001$), increasing markedly to 40,000 [6855–40,000] AU/ml post-booster ($P < 0.001$; Supplementary Tables S3, S4). No changes were observed for percent positivity status across T1–T4 (Fig. 1C).

The median IL-2 stimulation index levels were lower at T3 than T2 ($P = 0.023$) but not the IFN-γ stimulation index levels ($P = 0.552$) between both timepoints (Fig. 1D–E, Supplementary Table S3). Notably, IFN-γ stimulation index levels were higher at T4 than T2. No changes were observed when comparing the percent reactive pattern of the IFN-γ and/or IL-2 ELISpot assays across T1–T4, but the results were flawed due to the high number of invalid samples (Fig. 1F).

The GenID assay demonstrated that patients with IFN-γ-producing T cells had higher anti-SARS-CoV-2 spike antibody levels at T3 ($P = 0.028$, $n = 30$) but not the Abbott array ($P = 0.08$; $n = 28$). At T4, there was no significant difference for either assay (Abbott array: $P = 0.51$, $n = 17$; GenID assay: $P = 0.442$, $n = 17$). IL-2 could not be analyzed due to the low numbers on the reactive side at T3 ($n = 1$) and T4 ($n = 3$).

Patients with COVID-19 history had sustained higher anti-SARS-CoV-2 spike antibody levels (Abbott array) compared to infection-naïve patients at T2 ($n = 5$ vs. 53, respectively, total number = 58) ($P < 0.001$) and T3 ($n = 5$ vs. 35, respectively, total number = 40) ($P = 0.002$; Supplementary Table S5), although the booster conferred median IgG levels reaching the upper detection limit of 40,000 AU/ml in both groups at T4 ($n = 6$ vs. 36, respectively, total number = 42). Patients with COVID-19 history also had higher SARS-CoV-2-specific IFN-γ levels at T2 ($P < 0.001$), but not IL-2 ($P = 0.07$). No differences were seen in the IFN-γ SI levels at T3 ($P = 0.252$) and T4 ($P = 0.299$) between both groups (Supplementary Table S6). Given the high number of invalid samples of patients with COVID-19 history, the T3 and T4 IL-2 immune responses could not be analyzed.

Our results indicate a robust humoral immune response 6 months following primary COVID-19 vaccine cycle (> 90%), which is consistent with previous reports involving hemodialysis patients and healthy controls [3, 4]. However, while primary COVID-19 vaccine cycle resulted in markedly high anti-SARS-CoV-2 spike antibody levels (levels were highest in patients with previous COVID-19), the humoral response waned significantly within 6 months. IgG seropositivity, defined by commercially available tests, may overestimate the effectiveness of vaccine-induced humoral immunity, as the cutoff value that correlates with protection against SARS-CoV-2 infection is unknown. In contrast, we observed a sustained weak cellular immune response post-booster, although IFN-γ stimulation index levels increased significantly. Therefore, in line with previous works [4], antibody presence may not automatically correlate with functional cellular immunity, which is likely an important component in long-term protection against SARS-CoV-2. We and others have previously shown that cytokine induction during primary infection is associated with preferential induction of T cells producing IL-2, whereas reactivations are associated with T cells producing IFN [5]. This may also be applicable to booster vaccinations, as shown in the present study. Overall, our data indicate progressive waning of humoral immunity and a sustained weak cellular immune response within 6 months; the booster vaccination is able to substantially increase humoral immunity again; the emergence of SARS-CoV-2 variants with high potential for immune evasion may necessitate a further booster dose 4–6 months after the previous booster vaccination in dialysis patients.

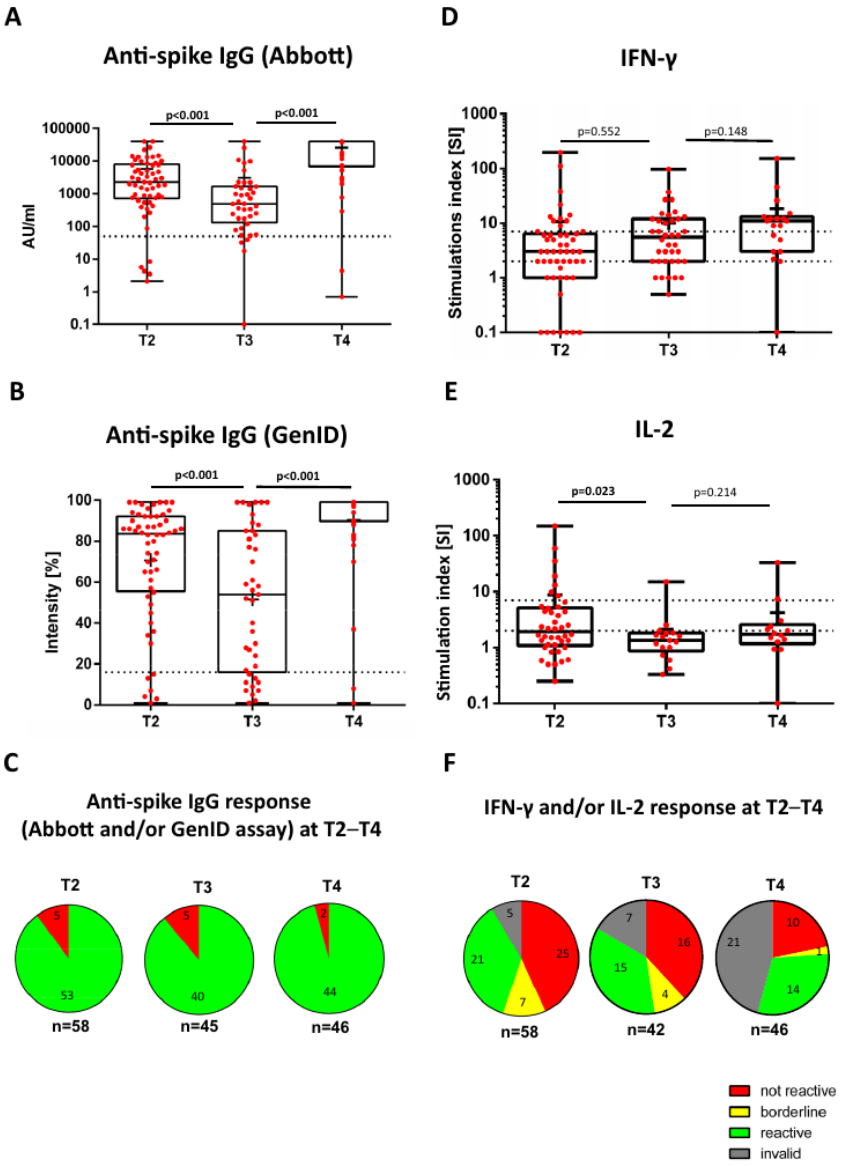

Fig. 1 Vaccine-induced anti-SARS-CoV-2 spike antibody detected using the Abbott array (**A**), GenID assay (**B**), and/or both (**C**), and SARS-CoV-2-specific T cell responses with secretion of IFN-γ (**D**), IL-2 (**E**), and/or both (**F**) at T2–T4. The figure depicts the cellular and humoral responses at 6 weeks (T2), 6 months (T3) after basic vaccination, and at 4 weeks (T4) post-booster. The humoral response level (as determined by the Abbott array and GenID assay) was lower at T3 compared to T2 ($P<0.001$) but increased post-booster ($P<0.001$). There was no reduction in the IFN-γ response between T2 to T3 ($P=0.552$) while the SARS-CoV-2-specific IL-2 response was reduced between both timepoints ($P=0.023$). No increase in cellular response (IL-2 or IFN-γ) was observed post-booster (p = NS). A logarithmic scale was used on the y-axis in panel A, D, and E. Due to the log scale, anti-SARS-CoV-2 spike antibody (Abbott array), IFN-γ, and IL-2 levels of zero are not displayed. The dashed horizontal lines indicate the cut-off for positivity (reactive; i.e., IgG > 50 AU/ml [Abbott array] and > 16% [GenID assay], IFN-γ and IL-2: SI ≥ 7); the area between the horizontal lines indicates the borderline zone used in each GenID assay. Bold values denote statistical significance at the $P<0.05$ level. *AU* arbitrary unit, *IFN-γ* interferon-γ, *IgG* immunoglobulin G, *IL-2* interleukin-2, *SARS-CoV-2* severe acute respiratory syndrome coronavirus type 2, *NS* not significant, *T2* timepoint 2, *T3* timepoint 3, *T4* timepoint 4

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Declarations

Compliance with ethical standards Approval by the local ethics committee (Ethikkommission des Fachbereich Medizin, Justus-Liebig-Universität Giessen) was granted before initiating enrollment (AZ 126/21). Written informed consent was obtained from the patients by a member of the research team.

Availability of data and material The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Competing interests KS is an employee of AID/GenID, the manufacturer of the ELISpot assay. None of the other authors declare any competing interests.

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Author contributions Study concept and design: HK, KS, CN, HS, CGS, MS, H-WB, and FH-S. FH-S is the senior author of the paper. Literature research and clinical advice: KS, VA, MA, KS, BC, IE, JC, CN, MW, HS, CGS, SJ, CR, WS, RW, MS, H-WB, and FH-S. Acquisition, analysis, or interpretation of data: KS, VA, MA, KS, BC, IE, JC, CN, MW, HS, CGS, SJ, CR, WS, RW, MS, H-WB, and FH-S. Drafting of the manuscript: HK, MA, KS, and FH-S. Critical revision of the manuscript for important intellectual content: KS, VA, MA, KS, BC, IE, JC, CN, MW, HS, CGS, SJ, CR, WS, RW, MS, H-WB, and FH-S. Preparation of figures: KS. Statistical analysis: MA. Study supervision: HK, H-WB, and FH-S. The authors shared study design, data collection, data analyses, and data interpretation, as well as preparation, review, and approval of the manuscript. The authors declare that the results presented in this paper have not been published previously in whole or part. The corresponding authors had full access to all study data and had final responsibility for the decision to submit for publication.

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5. ABKÜRZUNGSVERZEICHNIS

CERAD	= Consortium to Establish a Registry for Alzheimer's Disease
CKD	= chronische Niereninsuffizienz
COVID-19	= Coronavirus-19-Erkrankung
CVD	= kardiovaskuläre Erkrankungen
EMA	= European Medical Agency (Europäische Arzneimittelagentur)
GDS	= geriatrische Depressionsskala
GFR	= glomeruläre Filtrationsrate
HADS-D	= Hospital Anxiety and Depression Scale – Deutsche Version
HHNA	= Hypothalamus-Hypophysen-Nebennieren-Achse
MADRS	= Montgomery-Åsberg Depression Rating Scale
MMST	= Mini-Mental-Status-Test
MoCA	= Montreal-Cognitive Assessment
RBANS	= Repeatable Battery for the Assessment of Neuropsychological Status
SARS-CoV-2	= Schweres akutes respiratorisches Syndrom Coronavirus-2
SD	= Standard Deviation (Standard Abweichung)

6. LITERATURVERZEICHNIS

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