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厚生労働科学研究費補助金

腎疾患政策研究事業

慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

令和５年度　総括･分担研究報告書

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総括研究報告書

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研究要旨：本研究の目的は、前班で得られた多職種連携の実証研究を踏まえ、追加解析や教育資材の収集・分析により、有効な教育プログラムを開発し、最終的に多職種連携の戦略案を策定することである。今後のエビデンス実証研究の追加解析および追加研究および教育資材の収集・とりまとめによって、効果的な介入方法が明らかになり、これらを基盤に標準的な教育プログラムを作成することができれば、我が国のチーム医療の診療水準向上につながり、治療目標の達成率の向上を通じて、最終的にはCKD重症化予防とCKD患者のQOL改善、医療費節減が図れると期待される。

A. 研究目的：

我が国の慢性腎臓病(CKD)患者は1300 万人以上と推定され、ハイリスク群を形成している。CKD の重症化予防の基本は生活習慣の適正化と治療目標の遵守であるが、これらは腎臓専門医だけでは対処が難しく、かかりつけ医との医療連携、看護師・管理栄養士・薬剤師等との多職種連携が必須となる。これまでの取り組みにより、多職種連携に関する一定のエビデンスが得られたが、一般外来診療における多施設研究はなく、さらに、具体的にどのような患者に、どのように介入するのが効果的かは明らかになっていない。

本研究の目的は、前班で得られた多職種連携の実証研究を踏まえ、追加解析や教育資材の収集・分析により、有効な教育プログラムを開発し、最終的に多職種連携の戦略案を策定することである。本研究班は、進行中の厚生労働省研究班（柏原・岡田班）や日本腎臓病協会、コメディカルの関連3団体、日本糖尿病学会とも連携し、CKD対策に係る職種横断的なオールジャパン体制を構築する。

B. 研究方法：

本研究では、以下の研究計画・方法にしたがって、多職種介入研究の追加解析を行いつつ、必要に応じて追加研究実施し、効果的な介入方法を探る。また、多職種研究に参加した施設を中心に得られた教育資材を分析することを通じて、効果的な多職種による教育方法が何かを検討し、最終的に、標準的な教育プログラムを開発する。同時にこれを普及する基盤作りも進め、マニュアルへの反映や課題解決への提言を行ってゆく。

1) **多職種連携のエビデンス構築の継続**（阿部、岡田、内田、石川、竹内）：

多職種連携による生活指導・食事指導等がCKDの予防・重症化予防に有効かどうかを検証するための実証研究の成果（R2～R4年度多職種研究班）を踏まえ、追加解析を行う。どのようなアプローチがどのアウトカムに有効か、どの職種あるいはどの患者群に有効かも検討する。医療経済的な有効性についても検討する。必要に応じて統計専門家にも加わっていただく。

2) **多職種による教育プログラムの開発と普及**（阿部、岡田、猪阪、金崎、内田、石川、竹内）：

多職種介入の方法・資材は施設により様々であるため、R2～R4年度の実証研究の実施施設を中心に、介入方法・資材の収集を進める。これらのうち、とくに有効な成果の得られた介入方法の分析により、効果的な教育プログラムを検討、作成し、標準化プログラムを開発する。完成後はこれらの普及を図るため、HPによる公表、マニュアルや戦略案等への反映を検討、実施する。

3) **マニュアル作成と有効活用の推進**（岡田、柏原、金崎、内田、石川、竹内）：

前研究班で作成したCKD多職種連携マニュアルの有効活用、普及に努める。また、「腎臓病療養指導士のためのCKD指導ガイドブック」の改訂に際して、本研究班のCKD多職種連携マニュアルや標準化教育プログラムを反映できるよう、連携して検討を進める。

4) **ホームページ等による成果の公表**（金崎、柏原、岡田、要）：

研究班のホームページを充実させる。本研究班の取り組みから得られた成果やコンテンツをHP等で公表することにより、全国的な周知と普及を目指す。

5) **課題解決のための戦略案策定**（要、柏原、岡田、猪阪、阿部、金崎、内田、石川、竹内）：

得られた成果をもとに課題解決へ向けた戦略案を策定し、具体的な成果目標を示す。これらを提言として公表する。

（倫理面への配慮）

各臨床研究は、実施施設の倫理委員会の承認のもとに進め、個人情報にも十分な配慮のもとに進めている。

C. 研究結果：

前研究班の実証研究の中心メンバーからなるワーキンググループを組織した。WEB会議にて、前班で得られた多職種連携の実証研究を踏まえた実証研究の追加解析・二次調査案の策定を開始した。

（ワーキンググループメンバー）

・要　伸也、阿部雅紀

・櫻田 勉、今村吉彦、八田 告（研究協力者）

1) **多職種連携のエビデンス構築の継続**

① ワーキンググループで提案された追加解析案は以下の通りである。

- ✓ 介入効果は何によるか？　服薬アドヒアランスの改善、投与薬剤の違い、減塩効果(食事療法)、通院頻度、ドロップアウト率、などが候補となる。これらのうち、追加解析なものは検討を行い、新たなデータ収集が必要なものは追加研究を立案する。
- ✓ 施設ごとの介入効果の違いと関連する因子はないか？とくに効果の大きなモデル施設と小さな施設が何かを明らかにする。
- ✓ 効果はどこまで持続するかを明らかにするために追跡調査を行う。
- ✓ 介入前の状況(腎臓専門医単独の診療、非専門医で院内からの紹介、非専門医でかかりつけ医からの紹介、のどれか)
- ✓ 入院介入であれば外来でのチーム医療実施状況を調査する。

今後は、これらのうち、ワーキングループで継続検討し、実際に測定可能かつ重要な項目案を選択後､24施設との合同会議を開催のうえ追加解析、追加研究案を確定する方針である。

② 同時に、最適な教育プログラムの作成に必要な介入方法や教育資材の収集を行った

（資料 1）。今後は、これらから推奨される教育プログラムの素案を作成しつつ、①の結果を踏まえてプログラムの改良を行ってゆく。

2) **多職種による教育プログラムの開発と普及**：実証研究の参加施設から介入方法と教育資材を収集する。その後、1）の分析結果も踏まえ、多職種による効果的な標準教育プログラムを開発する。
3) **マニュアル作成と有効活用の推進**：2）で作成した教育プログラムを普及させる。前研究班で作成した「CKD ケアのための多職種連携マニュアル」などにもこれを反映させるようにする。
4) **ホームページ等による成果の公表**：得られた成果・コンテンツを HP 等で公表することにより、全国的な周知と普及を目指す。
5) **課題解決のための戦略案策定**；以上 1)～4)をもとに課題解決へ向けた戦略案を策定する。

D. 考察

本研究班の取り組みにより、CKD患者に特有の健康課題に適合した多職種連携による生活・食事指導等のエビデンスが強化され、多職種による療養指導方法の標準化を図ることができると期待される。すなわち、前研究班で実施した多職種連携実証研究の追加解析、および多職種による療養指導の実施プロトコールや教育資材の収集により、多職種連携の効果的な介入方法が具体的に明らかになり、教育プログラムの開発と標準化が可能になると考えられる。

さらに、これらの標準化教育プログラムをホームページやガイドブック等に反映させ、さらに、連携する厚生労働省研究班（柏原・岡田班）や日本腎臓病協会/腎臓病療養指導士委員会とも共有、発信することによって、効果的な多職種チーム医療の全国的な普及とチーム力の向上が進み、ひいてはCKD患者の生活習慣改善やセルフマネジメント力向上に繋げることができると期待される。また、多職種連携の実態把握によって地域差が明らかになれば、地域ごとに重点的な支援を行うことによって、多職種教育プログラムの全国普及と均霑化が図られると期待される。

E. 結論

今後のエビデンス実証研究の追加解析および追加研究および教育資材の収集･とりまとめによって、効果的な介入方法が明らかになり、これらを基盤に標準的な教育プログラムを作成することができれば､我が国のチーム医療の診療水準向上につながり､治療目標の達成率の向上を通じて、最終的には CKD 重症化予防と CKD 患者の QOL 改善、医療費節減が図れると期待される。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表
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45) シンポジウム:腎代替療法専門指導士における薬剤師の役割.腎移植における薬剤師の役割. 2023.10.28 第17回日本腎臓病薬物療法学会学術集会.
46) シンポジウム:腎移植後患者の服薬指導に必要なknow-how. 腎移植の免疫抑制療法-拒絶反応、感染症、副作用を最小化する最適な免疫抑制療法をめざして-. 2023.10.29 第17回日本腎臓病薬物療法学会学術集会.
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48) 竹内 裕紀. メディカルセミナー. シクロスポリンマイクロエマルジョン製剤におけるTDMの特性. 2023.11.04 第33回日本医療薬学会年会

H．知的財産権の出願・登録状況
1. 特許取得
該当なし

2. 実用新案登録
該当なし

3.その他
＜政策提言＞
◎分担研究者：内田明子
1) 日本医療政策機構（HGPI）腎疾患対策推進プロジェクト2023「患者・市民・地域が参画し、協働する腎疾患対策に向けて」アドバイザリーボードメンバー

◎分担者氏名：石川祐一
2) 日本医療政策機構腎疾患対策推進プロジェクト「腎疾患対策推進プロジェクト」アドバイザリーボードメンバー 「腎疾患対策推進プロジェクト 2023「患者・市民・地域が参画し、協働する腎疾患対策に向けて」政策提言・地方自治体における慢性腎臓病（CKD）対策好事例集

別添 5

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
岡田浩一、他	最新ガイドラインに基づく腎・透析診療指針2023-24序文、腎画像診断	岡田浩一	最新ガイドラインに基づく腎・透析　診療指針2023-24	総合医学社	東京	2023	22
岡田浩一、他	第13章高齢者CKD	丸山彰一	エビデンスに基づくCKD診療ガイドライン2023	東京医学社	東京	2023	149
岡田浩一	第1章3CKD：標準治療の理解と実践	南学正臣、高野秀樹	腎臓内科診療の掟	中外医学社	東京	2023	17
金﨑啓造	Ⅲ疾患各論 23 妊娠時の腎機能,妊娠高血圧症候群	柏原直樹,金子一成，南学正臣，柳田素子 編集	専門医のための腎臓病学 第3版	医学書院	東京	2023	533-545
金﨑啓造	Ⅲ各論　妊娠高血圧腎症	岡田浩一　編集	最新ガイドラインに基づく　腎・透析診療指針　2023-24	総合医学社	東京	2023	236-245
金﨑啓造	高浸透圧高血糖状態，乳酸アシドーシス	福井次矢，高木誠，小室一成編集	今日の治療指針2024	医学書院	東京	2023	752-753
金﨑啓造	第3章 腎保護効果のエビデンスとガイドライン 4.ミネラルコルチコイド受容体拮抗薬	阿部雅紀	糖尿病関連腎臓病（DKD）診療	日本医事新報社	東京	2023	119-124
竹内裕紀	第11章 薬物治療	日本腎臓学会	エビデンスに基づくCKD診療ガイドライン 2023	東京医学社	東京	2023	113-143
竹内裕紀	服薬指導・薬剤情報 腎血管性高血圧症		今日の治療指針　2024年度版	医学書院	東京	2024	626-627

竹内裕紀	臓器移植・造血幹細胞移植・輸血	編集：吉尾隆、鍋島俊隆、渡辺泰裕、早勢信正、賀川義之、大井一弥、丸山徹、篠原悦子、渡辺朋子、佐々木英久、野田幸裕、本屋敏郎、松尾和廣、高村徳人、唯野貢司	薬物治療学 改訂13版	南山堂	東京	2024	899-903

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発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Hirano A, Kadoya H, Yamanouchi Y, Kishi S, Sasaki T, Kashihara N.	IL-1β may be an indicator of peritoneal deterioration after healing of peritoneal dialysis-associated peritonitis.	BMC Nephrol.	24(1)	374	2023
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Matsuzaki K, et al.	Current treatment status of IgA nephropathy in Japan: a questionnaire survey.	Clin Exp Nephrol	27(12)	1032-1041	2023
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竹内裕紀	透析患者のくすりの疑問.血液透析患者の投与量調節の基本的な考え方	月間薬事	65(12)	2393-2397	2023
浦田元樹、竹内裕紀、古久保拓、平田純生	腎機能別薬剤投与法一覧	日本腎臓病薬物療法学会誌	2022-2023-No512(2)	1429-1804 251-347	2023
浦田元樹、竹内裕紀、古久保拓、平田純生	腎機能別薬剤投与法一覧	日本腎臓病薬物療法学会誌	2022-2023-No6 12(3)	1085-2169 403-506	2023
浦田元樹、竹内裕紀、古久保拓、平田純生	腎機能別薬剤投与法一覧	日本腎臓病薬物療法学会誌	2024-No1 13(1)	1-342 71-159	2024
浦田元樹、竹内裕紀、古久保拓、平田純生	腎機能別薬剤投与法一覧	日本腎臓病薬物療法学会誌	特別号改訂5版	1-502	2024

教育資材まとめ

	施設名	介入に加わった職種	介入方法	介入の内容	介入の時間	教育資材の有無 （＊は資材提供あり）	専門資格の有無 （療養士の介入、etc）
1	日産玉川病院	専門知識のある医師・看護師・管理栄養士・薬剤師（4職種）	同じ外来受診日に４職種が療養指導。 これを1セットとして、合計4セット実施。	職種毎にプログラムあり。	医師約15分、それ以外は１職種につき約３０分	あり＊	あり
2	日本大学医学部附属板橋病院	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種が療養指導。これを1セットとし、2～4セット実施。（最低2セット）	初回は看護師と管理栄養士は別々。2回目以降は初回の状況次第で合同で行う。	1職種15～30分(初回30～60分)。2回目以降は計30分。	あり＊	あり；看護師と管理栄養士は腎臓病療養指導士
3	奈良県総合医療センター	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種が療養指導。これを1セットとし、1セット実施。カンファレンスで不足があれば、2セット目を追加	看護師と管理栄養士は別々。	DVD	あり(DVD)＊	あり；管理栄養士は腎臓病療養指導士
4	明石医療センター	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種がCKD導は複数回実施することも多い（患者や主治医の意向によって決定）	看護師へ、主治医からの指導依頼内容を事前に伝達している。	医師は10～15分、看護師・管理栄養士は原則的に30分であるが変動あり。	あり＊	あり；管理栄養士のうち1名は腎臓病療養指導士
5	田附興風会医学研究所北野病院	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種がCKD療養指導。これを1セットとし、1～2セット実施。糖尿病透析予防指導では4回シリーズ。	看護師による生活指導と管理栄養士による栄養指導	医師は10分、それ以外は１職種につき30-60分	あり＊	あり；看護師と管理栄養士は腎臓病療養指導士
6	聖マリアンナ医大病院	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種がCKD療養指導。管理栄養士による栄養指導と看護師による生活指導（腎看護相談）は別日に実施。	患者のステージに応じた支援	医師は10-15分、それ以外は１職種につき30分	あり＊　（資材は教育入院用。栄養指導資材は同じものを外来でも使用）	あり；看護師と管理栄養士はほとんどが腎臓病療養指導士
7	聖マリアンナ医大横浜市西部病院	外来で多職種指導は実施できていない。医師より依頼がある時に栄養士が栄養相談実施。 尚、当院には腎臓病療養指導士取得の栄養士はいない。					
8	奈良県総合医療センター	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種がCKD療養指導。これを1セットとし、1セット実施。カンファレンスで不足があれば、2セット目を追加	看護師と管理栄養士は別々。	①管理栄養士（30分） ②看護師：DVD視聴（20分）、指導（30分） ③医師診察　10分	あり(DVD・紙)	あり；管理栄養士は腎臓病療養指導士
9	近江八幡市立総合医療センター	専門知識のある医師・看護師・管理栄養士（3職種）	蓄尿検査結果に基づき栄養指導間隔は変動、看護師指導は教育入院後3・6・12・24ヵ月で実施	減塩不良症例（自宅蓄尿）に管理栄養士による継続的な栄養指導、看護師による療養行動における患者行動変容の確認（患者アンケート実施）とその結果に基づく指導	1回15-30分程度	なし	あり；看護師と管理栄養士は腎臓病療養指導士
10	三思会東邦病院	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種がCKD療養指導。	看護師と管理栄養士が別々に指導。看護師は腎代替療法について説明、栄養士はCKDに対する食事指導	1職種15～30分	冊子「腎不全治療選択とその実際」、DVD「守りたい あなたらしさ～透析とともに～」NPO法人腎臓サポート協会などを使用	あり
11	京都大学医学部附属病院	専門知識のある医師・管理栄養士（2職種）	外来受診日に栄養指導を受けて頂く。回数は設定していない。	外来日に合わせて栄養指導をセットし、継続的に指導する。	1職種15分。	なし	あり
12	順天堂大学医学部附属練馬病院	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に3職種がCKD療養指導。これを1セットとし、2～4セット実施。（最低2セット）	初回は看護師と管理栄養士は別々。2回目以降は初回の状況次第で合同で行う。	1職種15～30分(初回30～60分)。2回目以降は計30分。	あり＊	あり；看護師と管理栄養士は腎臓病療養指導士
13	長崎大学病院腎臓内科	専門知識のある医師・看護師・管理栄養士（3職種）	外来受診日に医師・看護師でCKD療養指導、必要時管理栄養士を交える(1-2回)。	CKDや透析内容の説明、食事内容の確認。問題があれば栄養士の介入。希望時透析の見学・デモ。	合計30～60分程度	なし	あり
14	大阪公立大学医学部附属病院	糖尿病の透析予防外来として実施（依頼あればCKDも対応）	毎週月曜日に3職種で指導。３ヶ月に１回の頻度で4回を1クール（１年）で一通りの内容を説明。希望があれば繰り返す。	添付する資料をもとに、担当の看護師、管理栄養士から指導	1職種15～30分。	あり＊	あり；（糖尿病・腎臓）専門医・専任看護師・管理栄養士
15	藤枝市立総合病院	専門知識のある医師・透析室看護師・管理栄養士（3職種）	外来日に3職種が療養指導。透析室看護師が家人同伴で初回，eGFR30未満，eGFR15未満の最低3回は行い、以降は患者の病態、理解度、家庭環境などに応じて適宜追加。	栄養指導：管理栄養士が腎臓内科外来受診の待ち時間に実施。 CKD指導：透析室看護師が、3分冊のCKD指導テキストに基づき指導	医師の指導は外来診療時間 栄養指導は20－30分 CKD指導は30－60分	あり＊ 3分冊のCKD指導テキスト	あり；看護師と管理栄養士は腎臓病療養指導士を含む
16	医療法人埼友会　　埼友草加病院	専門知識のある医師・看護師・管理栄養士・薬剤師・公認心理師・社会福祉士（6職種）	主にCKDステージG4から介入。外来受診毎に職種（医師・看護師・管理栄養士）がCKD療養指導。必要に応じて他の職種も介入・指導	初回は看護師が介入し患者背景を把握する。その状況に応じて初回当日もしくは次の受診時に管理栄養士・薬剤師が介入	医師は10～20分。看護師初回30～60分。他職種含め2回目以降は各20～30分程度	あり	あり；看護師、管理栄養士は腎臓病療養指導士、薬剤師は日本腎臓病薬物療法認定薬剤師

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ORIGINAL ARTICLE

Effectiveness and current status of multidisciplinary care for patients with chronic kidney disease in Japan: a nationwide multicenter cohort study

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Abstract

Background Multidisciplinary care is well established in clinical practice, but its effectiveness in patients with chronic kidney disease (CKD) remains unclear. The aim of this study was to determine whether multidisciplinary care could help to avoid worsening kidney function in patients with CKD.

Methods This nationwide study had a multicenter retrospective observational design and included 3015 Japanese patients with CKD stage 3–5 who received multidisciplinary care. We assessed the annual decrease in estimated glomerular filtration rate (ΔeGFR) and urinary protein in the 12 months before and 24 months after the start of multidisciplinary care. All-cause mortality and initiation of renal replacement therapy were investigated according to baseline characteristics.

Results Most of the patients had CKD stage 3b or higher and a median eGFR of 23.5 mL/min/1.73 m^2. The multidisciplinary care teams consisted of health care professionals from an average of four disciplines. ΔeGFR was significantly smaller at 6, 12, and 24 months after initiation of multidisciplinary care (all $P < 0.0001$), regardless of the primary cause of CKD and its stage when multidisciplinary intervention was started. Urinary protein level also decreased after initiation of multidisciplinary care. After a median follow-up of 2.9 years, 149 patients had died and 727 had started renal replacement therapy.

Conclusion Multidisciplinary care may significantly slow the decline in eGFR in patients with CKD and might be effective regardless of the primary disease, including in its earlier stages. Multidisciplinary care is recommended for patients with CKD stage 3–5.

Trial registration UMIN00004999.

Keywords Certified Kidney Disease Educator · Chronic kidney disease · Estimated glomerular filtration rate · Kidney function · Multidisciplinary care · Renal replacement therapy

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Introduction

The number of patients with chronic kidney disease (CKD) is growing around the world. Approximately 13.3 million adults in Japan were estimated to have CKD in 2005 [1], and this number had increased to 14.8 million by 2015, potentially reflecting the aging population in Japan [2]. Accordingly, the number of patients with end-stage kidney disease starting renal replacement therapy (RRT) in Japan is increasing annually and the number of patients who are undergoing dialysis therapy now exceeds 340,000 [3]. The prevalence of dialysis in Japan is 2682 per million population, which is the second highest worldwide after Taiwan [4]. There are numerous risk factors for progressive CKD, including hypertension, diabetes, and advancing age, which result in worsening kidney function that can lead to end-stage kidney disease and cardiovascular disease (CVD). CKD is an internationally recognized public health problem because of its epidemiological features, high mortality rate, and considerable medical costs [5]. Therefore, important treatment goals in patients with CKD are slowing of disease progression, minimizing complications, and improving quality of life.

The multidisciplinary care model encompasses a range of disciplines with different but complementary skills, knowledge, and experience and aims to improve health care and achieve optimal outcomes in terms of the physical and psychosocial needs of patients [6]. However, there is still a need to improve the standard care for patients with CKD in clinical practice. The Certified Kidney Disease Educator (CKDE) system was established in Japan by the Japan Kidney Association (JKA) in 2017 with the aims of preventing progression of CKD and improving and maintaining patients' quality of life. Nurses, registered dietitians, and pharmacists who meet certain requirements are eligible for qualification as a CKDE. All CKDEs have acquired the basic skills for management of patients with CKD, including guidance on lifestyle modification, dietary counseling, and medical therapy according to stage of CKD. Thus, CKDEs play an important role in multidisciplinary care. By 2022, there were 1935 CKDEs in Japan, and multidisciplinary care of patients with CKD by board-certified nephrologists and CKDEs has become widespread. However, only a limited number of studies in Japan have investigated the association between multidisciplinary care for patients with CKD and kidney function, and these studies involved small numbers of patients from single centers [7, 8]. In this multicenter cohort study, we investigated the current status of multidisciplinary care for patients with CKD and whether multidisciplinary care can help to avoid worsening of kidney function in patients with CKD.

Methods

Study design and participants

This nationwide study was designed as a multicenter retrospective observational cohort study involving approximately 3000 Japanese patients who were enrolled at 24 selected medical institutions in Japan. Patients with CKD who received continuous multidisciplinary care between January 2015 and December 2020 and had kidney function data available for the 12 months before and the 24 months after receiving multidisciplinary care were included.

The following exclusion criteria were applied: age younger than 20 years; estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min/1.73 m^2; active malignant disease; transplant recipient status; history of long-term dialysis; and missing data on age, sex, or kidney function. The primary efficacy endpoint was the annual decline in eGFR (ΔeGFR) between 12 months before and 24 months after the start of multidisciplinary intervention. Secondary endpoints were the annual change in the urinary protein level between 12 months before and 24 months after the start of multidisciplinary intervention and the composite outcome of all-cause mortality and initiation of RRT until the end of 2021.

The study was approved by the ethics committee of Nihon University Itabashi Hospital and conducted in accordance with the Declaration of Helsinki, Japanese privacy protection laws, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare in 2015. The need for informed consent was waived due to the use of de-identified data. Information in this study was disclosed to subjects in an opt-out format. The study is registered in the University Hospital Medical Information Network (UMIN000049995).

Multidisciplinary care

Multidisciplinary care was defined as follows: (1) a care team comprising nephrologists and professionals from other disciplines, including nurses, registered dietitians, pharmacists, physical therapists, social workers, clinical engineers, and clinical laboratory technicians; and (2) an operational model of multidisciplinary care, whereby patients with CKD were managed medically, received patient education, and were encouraged to make lifestyle modifications according to the stage of CKD. The quality of the educational content provided was maintained in accordance with the recommendations of the Japanese Society of Nephrology, Japanese Society for Dialysis Therapy, Japan Society for Transplant, and Japanese Society for Clinical Renal Transplantation or the CKD Teaching Guidebook for Certified Kidney Disease Educators by the JKA [9, 10].

Data collection

Data were collected on patient demographics and clinical characteristics, including age, sex, history of CVD, primary etiology of CKD, body mass index (BMI), hemoglobin, serum albumin, blood urea nitrogen, creatinine (Cr), eGFR, urinary protein, and glycated hemoglobin (for patients with diabetes) at the time when multidisciplinary care intervention was initiated (baseline). CVD was defined as coronary artery disease, ischemic stroke, hemorrhagic stroke, and limb amputation. The eGFR was calculated according to the following formula for Japanese patients: eGFR (mL/min/1.73 m^2) = $194 \times$ serum $\mathrm{Cr}^{-1.094} \times \mathrm{age}^{-0.287} (\times 0.739$ for women) [11]. Urinary protein was calculated as the urinary protein to creatinine ratio (UPCR). The eGFR and UPCR values at 12 months before the intervention and at 6, 12, and 24 months after the start of the intervention were obtained. Information on the method and setting of intervention (outpatient or inpatient), duration of intervention (number of visits for intervention for outpatients or hospitalization days for inpatients), and type and number of staff was collected. The composite outcome of all-cause mortality and initiation of RRT was assessed using dates of death and initiation of RRT or the end of 2021 was reached, whichever came first. The type of RRT (i.e., hemodialysis, peritoneal dialysis, or kidney transplantation) was recorded.

Statistical analysis

Data are reported as the number and proportion, mean ± standard deviation, or median [interquartile range]. Categorical variables were examined using the chi-squared test, and continuous variables were compared using the *t* test. Three or more groups were compared using repeated-measures analysis of variance with Tukey's honestly significant difference test or the Kruskal–Wallis test, as appropriate. The associations between the number of multidisciplinary care team members and the number of interventions by the multidisciplinary care team, and the mean ΔeGFR and the % changes in UPCR were analyzed using Spearman's rank correlation coefficient. Incidence of all-cause death and incidence of initiation of RRT are presented as the number of events per 1000 person-years. For survival analysis of the composite outcome, the patients were divided into two groups according to diabetes mellitus (DM) status and four groups according to CKD stage (G3a, G3b, G4, or G5) at baseline. The composite outcome was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. A univariate analysis was performed according to eGFR stage, and multivariate survival analyses were performed using Cox proportional hazards models adjusted for confounders to examine associations between baseline CKD stage and the composite outcome during 6 years of follow-up. Model 1 was used to calculate the hazard ratios adjusted for basic characteristics, including age, sex, history of CVD, and DM status. Model 2 was the same as model 1 but was further adjusted for BMI, hemoglobin, serum albumin, and UPCR levels. A univariate analysis was performed according to DM status, and multivariate survival analyses using Cox proportional hazards models adjusted for confounding factors were performed to examine DM status and the composite outcome. Model 1 was used to calculate the hazard ratios adjusted for basic factors, including age, sex, and history of CVD, and model 2 was adjusted for BMI, hemoglobin, serum albumin, eGFR, and UPCR levels in addition to the factors included in model 1. The results from the models are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) and P-values. Multivariate survival analyses were performed using Cox proportional hazards models adjusted for confounders to examine associations between the number of multidisciplinary care team members and the number of multidisciplinary care team interventions and composite outcomes. Moreover, to discover which factors and specialty compositions within the multidisciplinary care team are advantageous for the composite endpoint, we estimated the HRs and compared them between the group with each specialist member present and the group without as the reference group. For the regression analyses, imputation of missing data was performed by conventional methods, as appropriate. All analyses were performed using JMP® version 13.0 (SAS Institute Inc., Cary, NC, USA). A *P* value < 0.05 was considered statistically significant.

Results

Patient characteristics at time of initiation of multidisciplinary care

Of 3146 patients registered during the study period, 131 were excluded (CKD stage 1 or 2, $n = 118$; no baseline kidney function data, $n = 13$), leaving 3015 patients for inclusion in the analysis. The patients' background characteristics are shown in Table 1. Mean age was 70.5 ± 11.6 years and 74.2% were male. In terms of disease severity, median eGFR was 23.5 [15.1–34.4] mL/min/1.73 m^2 and median UPCR was 1.13 [0.24–3.1] g/gCr. CKD was stage 4 in 1248 patients (41.4%), stage 3b in 761 (25.2%), and stage 5 in 726 (24.1%). Diabetic nephropathy was the most common primary cause of CKD, followed by hypertension and glomerulonephritis.

Interventions implemented by the multidisciplinary care team

Details of the interventions implemented by the multidisciplinary care team are shown in Table 2. Intervention was provided in an inpatient setting for more than half of the patients and on an outpatient basis for the remainder. The majority of the multidisciplinary team members were registered dieticians (90.4%), followed by nurses (86.2%), pharmacists (62.3%), and physical therapists (25.9%). The mean number of multidisciplinary care team members was four; 33.7% of the patients received intervention by five team members and 29.2% by four team members.

ΔeGFR before and after multidisciplinary care

The mean annual decline in eGFR (ΔeGFR) was − 6.0 ± 9.0 before multidisciplinary intervention and − 0.34 ± 5.78 at

Table 1 Baseline characteristics of the patients

Variable	
Patients, *n* (% male)	3015 (74.2)
Age, years	70.5 ± 11.6
Body mass index	24.2 ± 4.3
Serum creatinine, mg/dL	2.08 [1.48–3.14]
eGFR, mL/min/1.73 m^2	23.5 [15.1–34.4]
Blood urea nitrogen, mg/dL	32 [23–45]
Hemoglobin, g/dL	11.7 ± 1.9
Serum albumin, g/dL	3.7 ± 0.5
Urinary protein, g/gCr	1.13 [0.24–3.1]
Comorbid CVD, *n* (%)	885 (29.4)
HbA$_{1c}$ (in DM patients), %	6.4 ± 1.0
CKD stage, *n* (%)	
3 (3a + 3b)	1041 (34.5)
3a	280 (9.3)
3b	761 (25.2)
4	1248 (41.4)
5	726 (24.1)
Primary cause of CKD, *n* (%)	
Diabetes	1321 (43.8)
Hypertension	894 (29.7)
Glomerulonephritis	384 (12.7)
PCKD	88 (2.9)
Other	328 (10.9)

Data are shown as the number (percentage), mean ± standard deviation, or median [interquartile range]

Cr creatinine, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HbA$_{1c}$* glycated hemoglobin, *PCKD* polycystic kidney disease

Table 2 Characteristics of the multidisciplinary care team and interventions

Variable	
Place of intervention, *n* (%)	
Outpatient	1246 (41.3)
Inpatient	1769 (58.7)
Number of interventions	
Outpatient setting, *n*	4 [1–11]
Inpatient setting, *n*	7 [6–12]
Professional makeup of MDC team, *n* (%)	
Nurses	2600 (86.2)
Registered dieticians	2726 (90.4)
Pharmacists	1878 (62.3)
Physical therapists	781 (25.9)
Clinical laboratory technicians	178 (5.9)
Social workers	72 (2.3)
Other professionals	31 (1.0)
Number of MDC team members, *n* (%)	4 [3–5]
2	700 (23.2)
3	416 (13.8)
4	882 (29.2)
5	994 (33.0)
6	23 (0.8)

Data are shown as the number (percentage), mean ± standard deviation, or median [interquartile range]

MDC multidisciplinary care

6 months, − 1.40 ± 6.82 at 12 months, and − 1.45 ± 4.04 at 24 months after intervention (all $P < 0.0001$; Fig. 1). Furthermore, in the DM group, mean ΔeGFR was − 6.60 ± 9.5 before intervention and − 1.04 ± 5.92 at 6 months, − 2.28 ± 7.39 at 12 months, and − 2.06 ± 4.50 at 24 months after intervention (all $P < 0.0001$; Fig. 2a); the respective values in the non-DM group were − 5.55 ± 8.56, 0.20 ± 5.61, − 0.76 ± 6.29, and − 1.06 ± 3.66 (all $P < 0.0001$; Fig. 2b).

In patients with CKD stage 3, mean ΔeGFR was − 4.05 ± 9.19 before intervention and − 0.53 ± 6.84 at 6 months, − 1.82 ± 7.43 at 12 months, and − 1.83 ± 4.21 at 24 months after intervention; the difference was significant at all assessment points after intervention (Fig. 3a). When the patients with CKD stage 3 were divided into G3a and G3b subgroups, the difference in mean ΔeGFR was significant only for stage G3b (Supplementary Fig. 1). For patients with CKD stage 4, mean ΔeGFR was − 6.20 ± 8.35 before intervention and − 0.19 ± 5.01 at 6 months, − 1.33 ± 6.14 at 12 months, and − 1.54 ± 3.66 at 24 months after intervention (all $P < 0.0001$; Fig. 3b); the respective values in patients with CKD stage 5 were − 8.43 ± 9.13, − 0.33 ± 5.42, − 0.72 ± 6.98, and − 0.20 ± 4.36 (all $P < 0.0001$; Fig. 3c).

There was no significant correlation between the mean ΔeGFR and the number of multidisciplinary care team members, but there was a significant correlation between the mean ΔeGFR and number of interventions by the multidisciplinary care team at all time points (all $P < 0.05$; Supplementary Table 1).

Changes in proteinuria after multidisciplinary intervention

Median UPCR decreased significantly from 1.13 [0.24–3.10] g/gCr at baseline to 0.96 [0.23–2.63] g/gCr at 6 months ($P < 0.0001$), 0.82 [0.21–2.30] g/gCr at 12 months ($P < 0.0001$), and 0.78 [0.19–2.07] g/gCr at 24 months ($P = 0.019$) after intervention in all patients. There was a significant decrease in UPCR at all measurement times after intervention in the DM group but only at 6 months in the non-DM group ($P = 0.0003$) (Fig. 4).

There was a significant correlation between the % changes in UPCR and the number of multidisciplinary care team members at 12 and 24 months after intervention, but no significant correlation between the % changes in UPCR and the

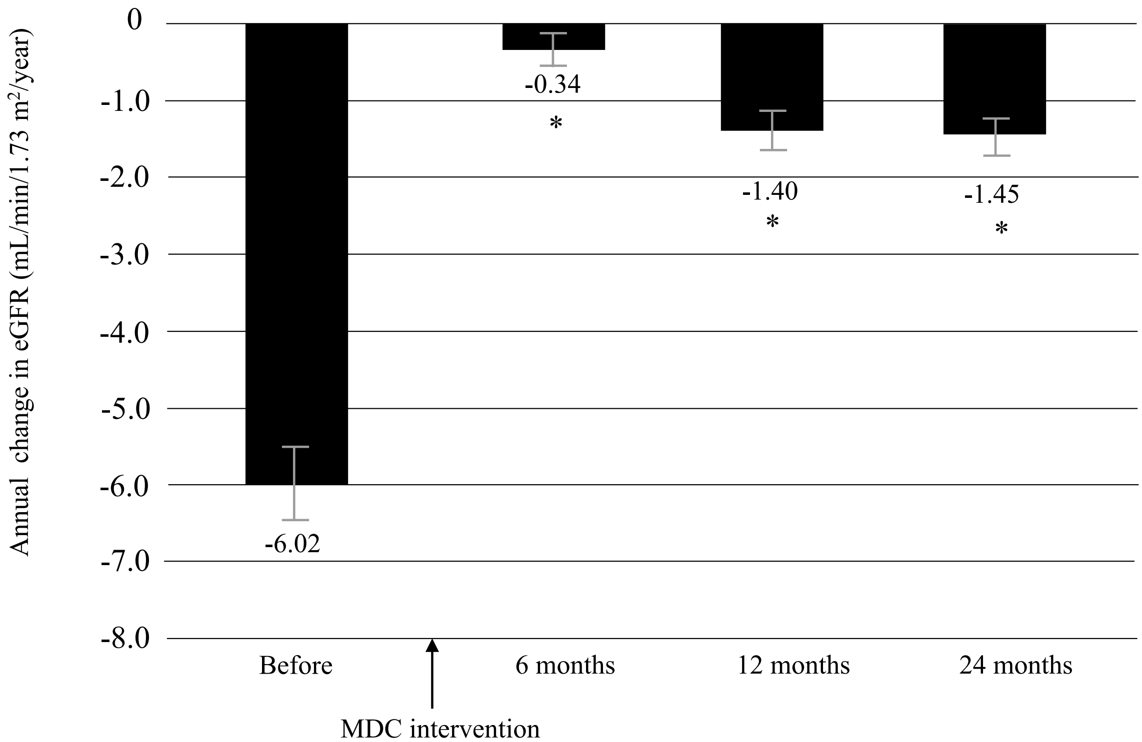


Fig. 1 Annual changes in eGFR decline (ΔeGFR) in the 12 months before and 24 months after initiation of multidisciplinary care in all patients. Data are shown as the mean. Bars indicate the 95% confidence interval. *$P < 0.0001$ vs. before start of MDC. eGFR estimated glomerular filtration rate, MDC multidisciplinary care

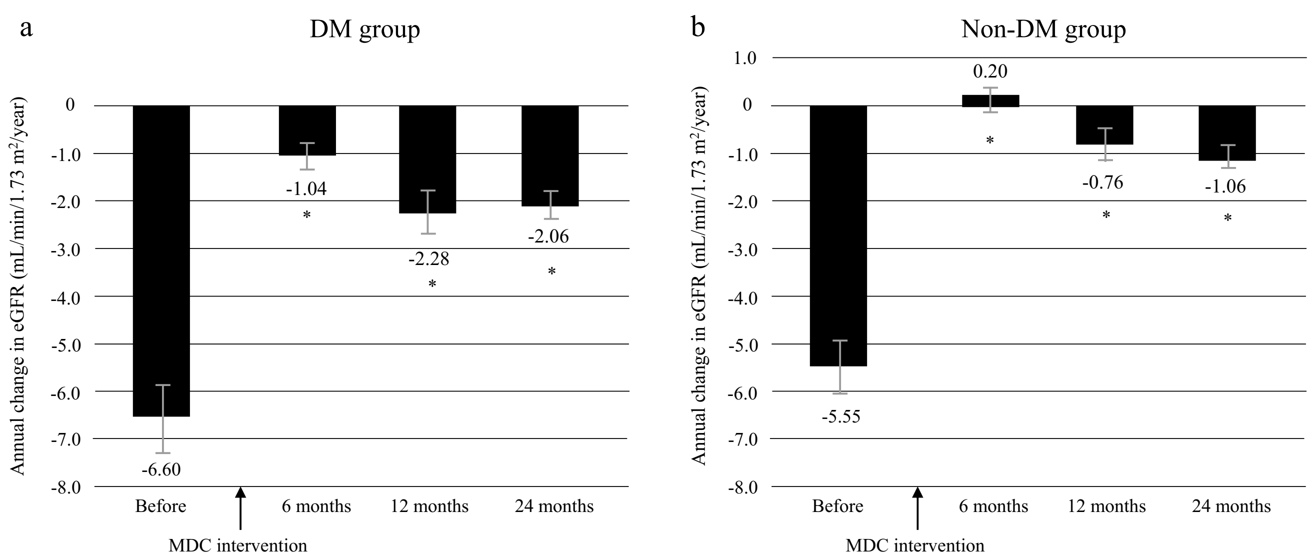


Fig. 2 Annual changes in eGFR decline (ΔeGFR) in the 12 months before and 24 months after initiation of multidisciplinary care according to DM status. **a** DM group, **b** non-DM group. *$P < 0.0001$ vs. before start of MDC. Data are shown as the mean. Bars indicate the 95% confidence interval. DM diabetes mellitus, eGFR estimated glomerular filtration rate, MDC multidisciplinary care

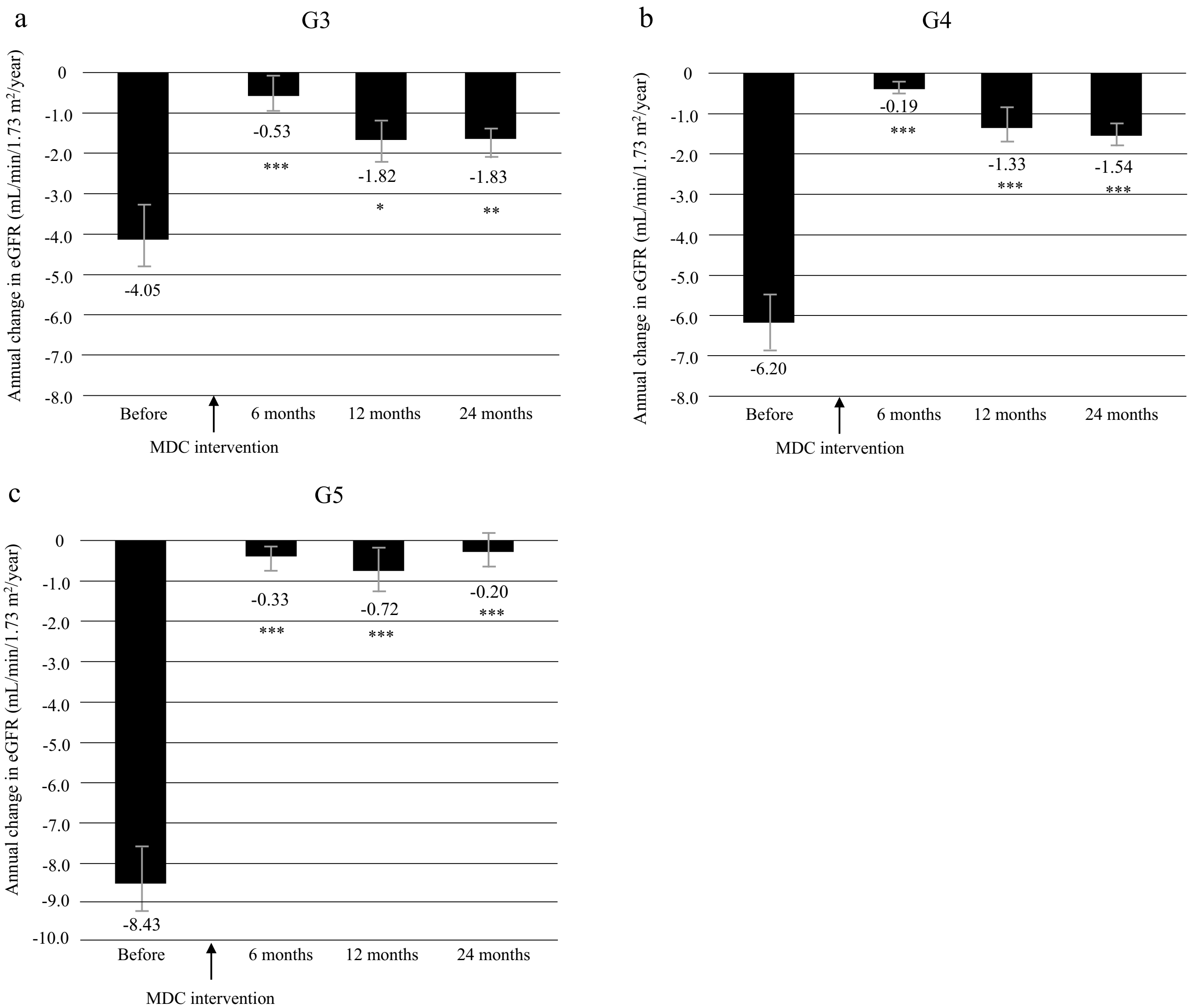


Fig. 3 Annual changes in decline of eGFR (ΔeGFR) in the 12 months before and 24 months after initiation of multidisciplinary care according to CKD stage at the time of initiation of MDC. **a** CKD stage G3, **b** CKD stage G4, **c** CKD stage G5. ***$P<0.0001$, **$P<0.001$, *$P<0.01$ vs. before start of MDC. Data are shown as the mean. Bars indicates the 95% confidence interval. CKD chronic kidney disease, eGFR estimated glomerular filtration rate, MDC multidisciplinary care

number of interventions by the multidisciplinary care team at all time points (Supplementary Table 2).

Outcomes

The median observation period was 35 [20–50] months, during which 149 patients (4.9%) died, 747 (24.8%) started RRT, and 66 (2.2%) were lost to follow-up. RRT consisted of hemodialysis in 618 patients (82.7%), peritoneal dialysis in 66 (8.8%), and renal transplantation in 25 (3.5%).

The characteristics and outcomes according to DM status are shown in Table 3. Patients in the DM group were more likely to be male, have comorbid CVD, be younger, and to have higher BMI and UPCR and lower eGFR and serum albumin levels. Kaplan–Meier analysis for the composite endpoint (all-cause mortality and initiation of RRT) revealed a significant difference between the DM and non-DM groups ($P<0.0001$, log-rank test; Fig. 5). Compared with the non-DM (reference) group, the DM group had a significant higher unadjusted HR for all-cause mortality and initiation of RRT (1.74, 95% CI 1.53–1.99, $P<0.0001$). After adjustment for background factors, including age, sex, and history of CVD, the HR in the DM group was 1.68 (95% CI 1.47–1.93, $P<0.0001$). After further adjustment for background factors and laboratory data, including BMI, hemoglobin, serum albumin, eGFR, and UPCR level at

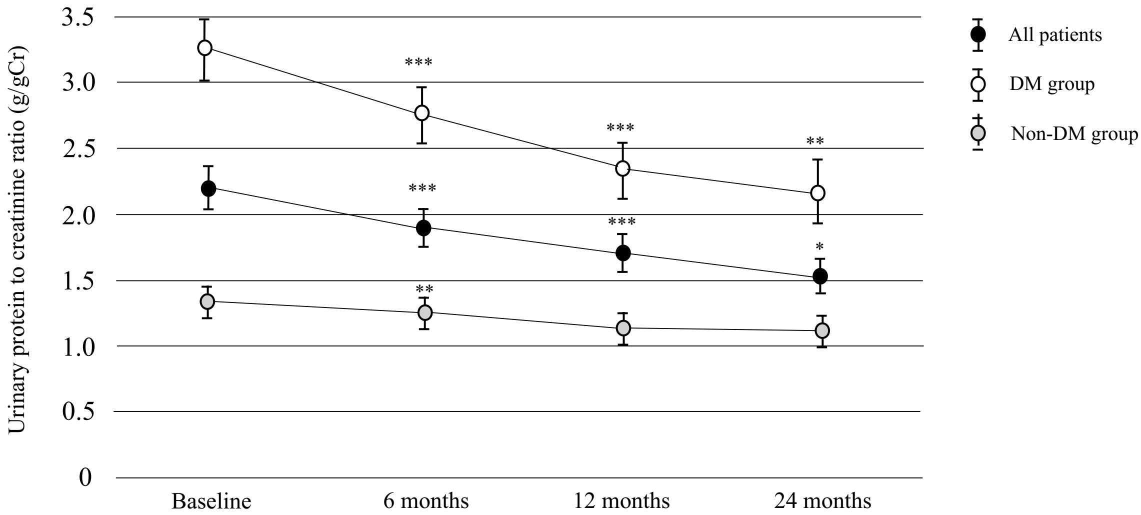


Fig. 4 Changes in urinary protein levels between the time of initiation of MDC and 24 months after initiation of multidisciplinary care according to DM status. ***$P < 0.0001$, **$P < 0.001$, *$P < 0.05$ vs. baseline. Data are shown as the mean. Bars indicates the 95% confidence interval. DM diabetes mellitus

Table 3 Baseline characteristics according to DM status

Variable	DM	Non-DM	*P* value
Patients, *n*	1321	1694	–
Male sex, %	78.1	71.2	< 0.0001
Age, years	69.4 ± 11.4	71.4 ± 11.7	< 0.0001
Body mass index	24.9 ± 4.7	23.7 ± 3.9	< 0.0001
Serum creatinine, mg/dL	2.65 ± 1.5	2.39 ± 1.4	< 0.0001
eGFR, mL/min/1.73 m^2	24.4 ± 12.5	26.5 ± 12.9	< 0.0001
Blood urea nitrogen, mg/dL	37.0 ± 17.5	35.7 ± 17.5	0.040
Hemoglobin, g/dL	11.5 ± 1.9	11.8 ± 1.9	< 0.0001
Serum albumin, g/dL	3.6 ± 0.6	3.8 ± 0.5	< 0.0001
Urinary protein, g/gCr	2.20 [0.57–4.90]	0.62 [0.15–1.79]	< 0.0001
Comorbid CVD, *n* (%)	436 (33.0)	449 (26.5)	0.0004
HbA_{1c} (in DM patients), %	6.6 ± 1.1	–	–
CKD stage, *n* (%)			0.0005
3 (3a + 3b)	406 (30.7)	635 (37.5)	
3a	106 (8.0)	174 (10.3)	
3b	300 (22.7)	461 (27.2)	
4	561 (42.5)	687 (40.6)	
5	354 (26.8)	372 (21.9)	
Observation period, months	33 [17–48]	36 [22–52]	< 0.0001
All-cause death, *n* (%)	75 (5.7)	75 (4.4)	0.132
All-cause death, per 1000 person-years	20.3	14.2	0.031
Initiation of RRT, *n* (%)	416 (31.5)	331 (19.5)	< 0.0001
Initiation of RRT, per 1000 person-years	113	62.8	< 0.0001

Data are shown as the number, percentage, mean ± standard deviation, or median [interquartile range]

Cr creatinine, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *RRT* renal replacement therapy

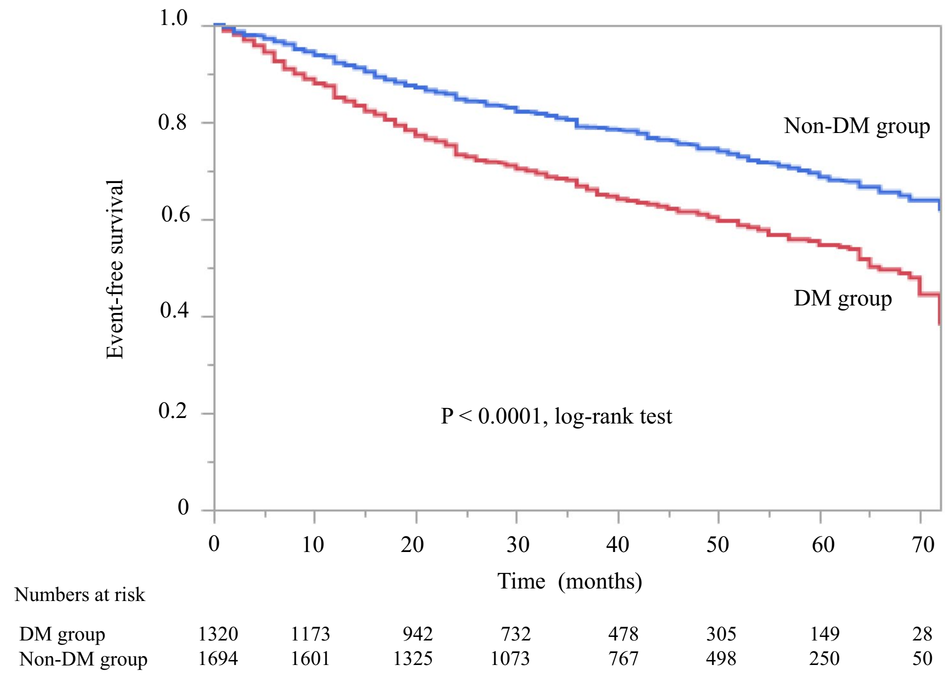


Fig. 5 Kaplan–Meier curves for the incidence of all-cause death and initiation of renal replacement therapy in Japanese patients with CKD according to DM status. CKD chronic kidney disease, DM diabetes mellitus

Table 4 All-cause mortality and initiation of renal replacement therapy according to DM status in Cox proportional hazards models adjusted for confounding factors in Japanese patients with CKD

Group	Unadjusted			Model 1			Model 2		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Non-DM	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
DM	1.74	1.53–1.99	<0.0001	1.68	1.47–1.93	<0.0001	1.28	1.09–1.51	<0.0001

Model 1 was adjusted for basic factors, including age, sex, and history of cardiovascular disease, and model 2 was adjusted in the same way as model 1 but with additional adjustment for body mass index, hemoglobin, serum albumin, estimated glomerular filtration rate, and urinary protein level at baseline

CI confidence interval, *CKD* chronic kidney disease, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HR* hazard ratio

baseline, the DM group had a significantly higher HR (1.28, 95% CI 1.09–1.51, $P<0.0001$) (Table 4). Kaplan–Meier analysis revealed a significant difference in all-cause mortality between the DM and non-DM groups ($P=0.031$, log-rank test; Supplementary Fig. 2). After adjustment for background factors, including age, sex, and history of CVD, the HR in the DM group compared with the non-DM group (reference) was 1.49 (95% CI 1.08–2.06). After further adjustment for background factors and laboratory data, including BMI, hemoglobin, serum albumin, eGFR, and UPCR level at baseline, the HR was significantly higher in the DM group (1.49, 95% CI 1.01–2.19, $P=0.044$) (Supplementary Table 3).

Patient characteristics and outcomes according to CKD stage are shown in Table 5. BMI, hemoglobin, the serum albumin level, and the glycated hemoglobin value (for patients with diabetes) decreased while the UPCR level increased with progression though the stages of CKD. All-cause mortality and the RRT initiation rate were dependent on the disease stage. Significant differences (all $P<0.0001$, log-rank test) were found in the composite endpoint (all-cause death or RRT initiation) according to CKD stage at baseline in Japanese patients with CKD (Fig. 6). Kaplan–Meier analysis revealed that all-cause mortality varied significantly depending on the CKD stage at baseline ($P=0.0009$, log-rank test; Supplementary Fig. 2). After adjustment for basic factors, including age, sex, history of CVD, and DM status, the HRs in the G3b, G4, and G5 groups when compared with the G3a (reference) group were 2.43 (95% CI 1.04–7.08), 2.49 (95% CI 1.11–7.17), and 3.77 (95% CI 1.61–11.0), respectively. However, after adjustment for basic factors and laboratory data, including BMI, hemoglobin, serum albumin, and UPCR level, only the G5 group had a significantly higher HR (3.03, CI 1.01–9.11, $P=0.048$; Supplementary Table 4).

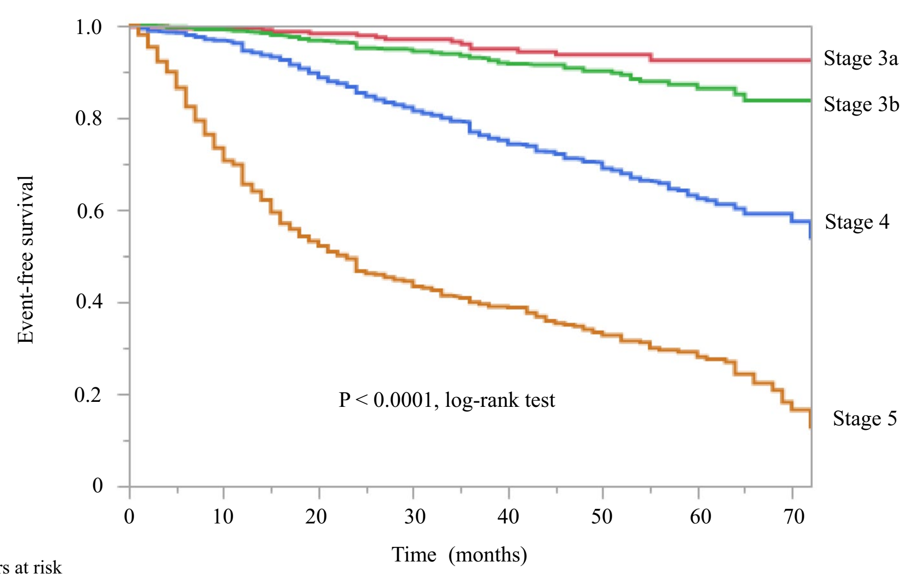
Table 5 Comparison of patient characteristics and outcomes according to CKD stage at baseline

Variable	Stage 3a	Stage 3b	Stage 4	Stage 5	*P* value
Patients, *n*	280	761	1248	726	–
Male sex, %	77.5	77.9	74.4	68.9	0.0005
Age, years	65.7 ± 12.1	70.3 ± 10.9	71.7 ± 11.6	70.6 ± 11.8	< 0.0001
Body mass index, kg/m^2	24.9 ± 4.3	24.2 ± 4.1	24.3 ± 4.4	23.7 ± 4.3	0.001
Serum creatinine, mg/dL	1.07 ± 0.14	1.44 ± 0.23	2.31 ± 0.53	4.44 ± 1.37	< 0.0001
eGFR, mL/min/1.73 m^2	51.0 ± 3.9	36.4 ± 4.2	21.8 ± 4.4	10.8 ± 2.7	< 0.0001
Blood urea nitrogen, mg/dL	18 [15–21]	23 [20–27]	34 [28–42]	53 [44–64]	< 0.0001
Hemoglobin, g/dL	13.7 ± 1.6	12.6 ± 1.8	11.4 ± 1.6	10.4 ± 1.5	< 0.0001
Serum albumin, g/dL	3.9 ± 0.5	3.9 ± 0.5	3.7 ± 0.5	3.6 ± 0.5	< 0.0001
Urinary protein, g/gCr	0.33 [0.08–1.32]	0.33 [0.09–1.43]	1.20 [0.32–3.21]	2.59 [1.26–4.98]	< 0.0001
Comorbid CVD, *n* (%)	71 (25.4)	211 (27.8)	394 (31.6)	209 (28.8)	0.0002
HbA1c (in DM patients), %	6.7 ± 1.1	6.5 ± 1.1	6.4 ± 1.0	6.2 ± 0.9	< 0.0001
Primary cause of CKD, *n* (%)					0.0024
Diabetes	106 (37.9)	299 (39.3)	561 (45.0)	354 (48.8)	
Hypertension	97 (34.6)	245 (32.2)	381 (30.5)	171 (23.6)	
Glomerulonephritis	39 (13.9)	97 (12.8)	146 (11.7)	102 (14.0)	
PCKD	6 (2.1)	24 (3.2)	35 (2.8)	23 (3.2)	
Other	32 (11.4)	95 (12.5)	125 (10.0)	76 (10.4)	
Observation period, months	44 [30–56]	40 [28–53]	36 [23–51]	29 [9–37]	< 0.0001
All-cause mortality, *n* (%)	5 (1.8)	37 (4.9)	69 (5.5)	39 (5.4)	< 0.0001
All-cause mortality, per 1000 person-years	5.0	14.6	17.8	25.4	< 0.0001
RRT initiation, *n* (%)	9 (3.2)	30 (4.0)	268 (21.5)	440 (60.6)	< 0.0001
RRT initiation, per 1000 person-years	8.9	11.8	69.1	278	< 0.0001

Data are shown as the number (percentage), mean ± standard deviation, or median [interquartile range]

Cr creatinine, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, HbA_{1c} glycated hemoglobin, *PCKD* polycystic kidney disease, *RRT* renal replacement therapy

Fig. 6 Kaplan–Meier curves for the incidence of all-cause death and initiation of renal replacement therapy initiation at baseline in Japanese patients with CKD according to CKD stage. CKD chronic kidney disease



Numbers at risk

Stage 3a	280	279	248	213	160	110	60	14
Stage 3b	760	754	646	541	364	244	106	19
Stage 4	1248	1208	1022	787	535	337	175	34
Stage 5	726	533	364	268	169	112	58	11

Table 6 Cox proportional hazard ratios of the associations of the number of multidisciplinary care team members and the number of interventions by the multidisciplinary care team with the composite endpoint

Variables	HR	95% CI	*P* value
Number of MDC team members (increase by 1)	0.85	0.80–0.89	< 0.0001
Number of interventions by MDC team (increase by 1)	0.97	0.96–0.98	< 0.0001

CI confidence interval, *MDC* multidisciplinary care, *HR* hazard ratio

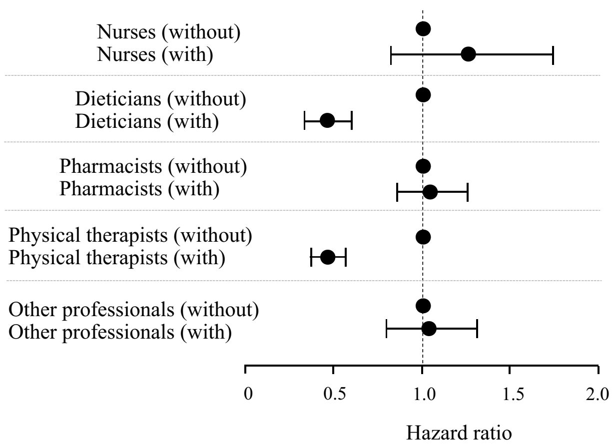


Fig. 7 Association between specialty composition of the multidisciplinary care team and composite endpoint stratified by with or without the presence of each professional on the team. Circles indicate the adjusted hazard ratio (HR) for all-cause mortality and initiation of renal replacement therapy. Error bars indicate 95% confidence intervals (CI). The HR for the composite endpoint (95% CI) was derived from Cox proportional hazards models adjusted for all covariate values, including age, sex, history of cardiovascular disease, the presence or absence of diabetes, body mass index, hemoglobin, serum albumin, and urinary protein levels at baseline

There was a significant association between the number of multidisciplinary care team members and the composite endpoint. The HR decreased significantly with increasing numbers of multidisciplinary care team members. Also, there was a significant association between the number of interventions by the multidisciplinary care team and the composite endpoint; that is, the prognosis of the composite outcome improved as the number of interventions increased (Table 6). When we compared composite endpoints according to the specialty composition of the multidisciplinary care team, there were significantly lower HRs when registered dietitians (HR 0.47, 95% CI 0.35–0.63, $P < 0.0001$) and physical therapists (HR 0.39, 95% CI 0.31–0.48, $P < 0.0001$) were included in the multidisciplinary care team (Fig. 7).

Presence of diabetes, being a male, history of CVD, hemoglobin, eGFR, and UPCR levels at baseline and interventions by registered dieticians and physical therapists were all identified as independent predictors of the composite outcome using multivariate Cox proportional hazard regression analysis (Table 7).

Discussion

Our nationwide cohort study included 3015 individuals from 24 facilities in Japan, 22 (91.7%) of which employ CKDEs and these 22 facilities provided intervention to 98.2% of all participating patients. Thus, the major strengths of this study are its large sample size recruited from multiple centers. Moreover, the observation period was relatively long, and a comparatively high number of elderly patients were included. Although the mean age of patients in the previous studies was younger than 70 years, our mean age was 70.5 years, reflecting our aging CKD population in Japan [12]. This study is the first to indicate that multidisciplinary care of CKD in Japan may be able to prevent worsening kidney function regardless of the underlying etiology. Multidisciplinary care was effective for patients with CKD regardless of whether they had DM. Furthermore, multidisciplinary care might be effective in the earlier stages of CKD. A multidisciplinary care team should include a nephrologist, nurse, and professionals from other fields and is recommended for patients with CKD stage 3–5. Our results suggest that the greater the number of professionals in a multidisciplinary care team, especially registered dietitians and physical therapists, the greater the number of interventions provided, which likely improves prognosis. Moreover, Japanese patients with CKD have an overwhelmingly higher rate of initiation of RRT than of mortality. The incidence of all-cause mortality in our patients with stage 3–5 CKD increased as eGFR declined but at a very low rate at all CKD stages under multidisciplinary care.

In addition to treatment and management of CKD, various lifestyle adjustments and self-management behaviors are required from the early stage of CKD through to the time of initiation and maintenance of RRT. Patients with CKD require holistic care and support, including dietary modification, maintenance and improvement of medication adherence, self-monitoring, early detection of complications, and the financial resources needed to continue treatment. Such support cannot be provided by medical staff alone and must be carried out by a medical team consisting of multiple professionals. To achieve good outcomes, multidisciplinary care teams that include nephrologists,

Table 7 The multidisciplinary care team's multivariate Cox proportional hazard ratios of the variables connected to the composite endpoint

Variables	HR	95%CI	*P* value
Age (increase by 1 year)	0.99	0.97–1.01	0.095
Sex (male)	1.25	1.06–1.48	0.009
Diabetes (yes)	1.34	1.14–1.58	0.0003
Comorbid CVD (yes)	1.30	1.13–1.49	0.0002
Body mass index (increase by 1 kg/m^2)	0.98	0.95–1.00	0.063
Hemoglobin (increase by 1 g/dL)	0.90	0.86–0.95	0.0002
Albumin (increase by 1 g/dL)	0.91	0.77–1.07	0.275
Baseline eGFR (increase by 1 ml/min/1.73m^2)	0.91	0.90–0.92	< 0.0001
Baseline urinary protein (increase by 1 g/gCr)	1.08	1.05–1.11	< 0.0001
Nurses (yes)	0.89	0.55–1.42	0.617
Dieticians (yes)	0.49	0.36–0.66	0.035
Pharmacists (yes)	1.07	0.92–1.27	0.361
Physical therapists (yes)	0.46	0.22–0.93	0.017
Other professionals (yes)	0.91	0.62–1.33	0.651

CI confidence interval, *Cr* creatinine, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *HR* hazard ratio

nurses, registered dietitians, pharmacists, physical therapists, occupational therapists, and medical social workers should be involved and have shared goals for individual patients.

Multidisciplinary care has been shown to decrease all-cause mortality, reduce the need for temporary catheterization for dialysis, and decrease the hospitalization rate in patients with CKD [13–16]. In contrast, some studies have not identified significant differences in these variables according to whether patients receive multidisciplinary care [17–19]. However, a meta-analysis revealed that multidisciplinary care could decrease all-cause mortality in patients with CKD, reduce the need for temporary catheterization in patients receiving dialysis, and decrease the hospitalization rate, but only in patients with stage 4–5 disease [12]. Moreover, the CKD-JAC study found that all-cause mortality and cardiovascular event rates were lower in Japanese patients with CKD who are under the care of a nephrologist than in their Western counterparts [20–22]. The lower mortality rate in our study is consistent with the findings of the previous studies. It is thought that Japanese patients with CKD who are under the care of a nephrologist with strict management of blood pressure, metabolism, and blood glucose are at much lower risk of cardiovascular events and death than patients with CKD in Western countries, although racial differences may affect the risk [20]. Further research is needed to determine whether clinical outcomes are better in patients who receive multidisciplinary care than in those who are cared for by nephrologists alone.

The composition of the participating multidisciplinary care teams varied greatly from facility to facility in this study. It has been reported that the ideal multidisciplinary care model for patients with CKD consists of a nurse, dietician, pharmacist, and social worker in addition to a nephrologist [23]. Although some studies have found no significant difference in all-cause mortality between multidisciplinary care and non-multidisciplinary care when the multidisciplinary team included a nephrologist and a nurse [17, 19], other studies have demonstrated a significant difference in all-cause mortality when the multidisciplinary team included a nephrologist, nurse, dietician, and pharmacist [15, 16]. A meta-analysis found no significant difference in all-cause mortality when the team included a nephrologist and a nurse [12]; however, all-cause mortality was lower if the team included a nephrologist, nurse, and health care professionals from other disciplines. The present study found that addition of a nurse or dietician compared to a nephrologist alone significantly slowed the decline in eGFR. Furthermore, recent studies have identified that a higher physical activity level can slow the decline in kidney function in patients with CKD [24–27]. A guideline for exercise therapy in patients with pre-dialysis CKD and those on dialysis has been published by the Japanese Society of Renal Rehabilitation [28]. Some of the facilities in our cohort include physical therapists in their multidisciplinary care teams. Further investigations are needed to determine which and how many health care professionals are required in a multidisciplinary care team to achieve the best outcomes.

In the aforementioned meta-analysis, there was no significant difference in the all-cause mortality or hospitalization rate according to whether multidisciplinary care was received in patients with CKD stage 1–5; however, multidisciplinary care decreased both all-cause mortality and the hospitalization rate in patients with CKD stage 4–5 [12]. It is known that all-cause mortality and hospitalization rates are associated with the stage of CKD, so patients with advanced CKD (stage 4–5) would have a higher rate of cardiovascular complications and higher risk of death and hospitalization because of decreasing kidney function. Therefore, the effect of multidisciplinary care on all-cause mortality is more difficult to demonstrate in short-term studies of patients with earlier stages of CKD, which may last 1–3 years, than in those with CKD stage 4–5, in whom the effect of multidisciplinary care would be more marked. Referral to a nephrologist is recommended for patients with CKD who reach stage 4 according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and for patients who reach stage 3b or higher according to the Japanese Society of Nephrology guidelines [29, 30]. However, the findings of our study, which included a long-term observation period of 6 years, suggest that multidisciplinary care can prevent worsening kidney function even in patients with stage 3 CKD.

The present study revealed that the reduction in proteinuria and improvement in ΔeGFR were seen in the DM group over a period of 24 months. Likewise, the improvement in ΔeGFR in the non-DM group was seen over 24 months, but the reduction in proteinuria was evident at just 6 months after starting multidisciplinary care. The rate of nephrosclerosis caused by hypertension in the non-DM group was high, reflecting the aging of the CKD population in Japan. Nephrosclerosis caused by hypertension is characterized by lower proteinuria and a slower decline in eGFR compared with diabetic nephropathy [31]. This was why we found a relationship between the reduction in proteinuria and the improvement in ΔeGFR in the DM group but not in the non-DM group. In addition, no significant difference in ΔeGFR was seen in the stage G3a group over the 24-month period. This may be because of a slower decline in eGFR, fewer or less frequent interventions, or proportionately fewer patients in stage G3a than in other stages. Therefore, the stage G3a group included patients who were not judged by nephrologists to require more intensive treatment via multidisciplinary intervention, since their eGFR values were relatively well preserved.

This study has several limitations. First, it did not include a control group. However, the previously reported meta-analysis found that multidisciplinary care was associated with a lower risk of all-cause mortality in cohort studies but not in randomized controlled trials [19]. Moreover, we could not confirm whether multidisciplinary care contributed to a decrease in the number of patients requiring dialysis. Therefore, further randomized controlled trials and large epidemiological studies that include control groups will be required to confirm the efficacy of multidisciplinary care in patients with CKD. Second, we did not investigate changes in prescriptions, blood pressure, body weight, glycemic control, or laboratory findings other than for kidney function. These factors, which can be influenced by multidisciplinary care, might play an important role in the improvement of both eGFR and proteinuria. It has been reported that the number of medications and prescription patterns among board-certified nephrologists in Japan did not change after the advent of multidisciplinary care [7, 8]. In addition, interventions by registered dieticians and physical therapists were identified as independent predictors of kidney outcomes. However, we could not evaluate what factors contributed most to improving kidney outcomes, such as whether the reduction of salt intake by registered dietitians or exercise therapy by physical therapists lowered blood pressure. Therefore, further investigations are needed to determine the contributing factors of improved adherence to prescription medications, dietary modification, and exercise therapies to prevent the worsening of kidney function. Finally, there may have been some degree of facility and selection bias as a result of variations in the types of health care professionals comprising the multidisciplinary care team and in the educational program between facilities as a result of differences in practice and patient populations. Therefore, educational programs should be standardized to improve the standard of treatment for patients with CKD and an effective and efficient care curriculum should be established.

In conclusion, our findings indicate that multidisciplinary care may significantly slow the decline of eGFR in patients with CKD and be effective regardless of the primary disease. Furthermore, they suggest that multidisciplinary care might be effective even in the earlier stages of CKD. Therefore, multidisciplinary care should be recommended for patients with CKD stage 3–5. Further research is needed to confirm that the CKDE system contributes to improving the standard of medical care for patients with CKD.

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Author contributions MA wrote the manuscript and analyzed the data. TH, YI, TS, and TM designed the study and contributed to data collection. MA, TH, YI, TM, and SK discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest MA is an associate editor of *Clinical and Experimental Nephrology.* The other authors declare that they have no other relevant financial interests. Publication of this report was not supported by any grants.

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KIDNEY RESEARCH AND CLINICAL PRACTICE

Examine the optimal multidisciplinary care teams for patients with chronic kidney disease from a nationwide cohort study

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Background: Multidisciplinary team-based integrated care (MDC) has been recommended for patients with chronic kidney disease (CKD). However, team-based specific structured care systems are not yet established. Therefore, we investigated the efficacy of MDC system and the optimal number of professionals that make up the team for maintaining kidney function and improving prognosis.
Methods: This nationwide, multicenter, observational study included 2,957 Japanese patients with CKD who received MDC from 2015 to 2019. The patients were divided into four groups according to the number of professionals in the MDC team. Groups A, B, C, and D included nephrologists and one, two, three, and four or more other professionals, respectively. Changes in the annual decline in estimated glomerular filtration rate before and after MDC were evaluated. Cox regression was utilized to estimate the correlation between each group and all-cause mortality and the start of renal replacement therapy (RRT) for 7 years.
Results: The change in eGFR significantly improved between before and at 6, 12, and 24 months after MDC in all groups (all $p < 0.0001$). Comparing group D to group A (reference), the hazard ratio (HR) for all-cause mortality and the start of the RRT was 0.60 (95% confidence interval, 0.48–0.73; $p < 0.0001$) after adjustment for multiple confounders. Lower HR in group D was confirmed in both diabetes and nondiabetes subgroups.
Conclusion: An MDC team comprised of five or more professionals might be associated with improvements in mortality and kidney prognosis. Furthermore, MDC might be effective for treating CKD other than diabetes.

Keywords: Certified kidney disease educator, Chronic kidney disease, Estimated glomerular filtration rate, Kidney function, Multidisciplinary care, Renal replacement therapy

Introduction

With the global population aging, the number of patients with chronic kidney disease (CKD) is increasing [1]. Between 2005 and 2015, the number and prevalence of CKD in the adult Japanese population increased from 13.3 mil-

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lion to 14.8 million and from 12.9% to 14.6%, respectively [2]. Diabetes, hypertension, old age, dyslipidemia, obesity, smoking, and lifestyle-related diseases are well known to increase the risk of CKD, which is not only the primary risk factor for end-stage kidney disease but also one of the most significant risk factors for cardiovascular disease (CVD) [3–5]. Delaying disease progression, reducing complications, and improving quality of life are the main objectives of CKD therapy. Therefore, multifactorial intervention, including blood pressure control and glycemic control, in combination with lifestyle modification and dietary advice, with multidisciplinary team-based integrated care, has been highlighted as an important therapeutic strategy to reach this objective [6].

The comprehensive treatment model is an interdisciplinary medical care system that integrates a variety of professions with different but complementary abilities, knowledge, and experience to improve healthcare and produce the best results to suit patients' needs both physically and psychologically [7,8]. In Japan, the Certified Kidney Disease Educator (CKDE) system was established by the Japan Kidney Association (JKA) in 2017 to prevent disease progression and improve and maintain the quality of life for patients with CKD [9]. Nurses, registered dietitians, and pharmacists who were trained and meet certain requirements are eligible for qualification as a CKDE [9]. However, even if multidisciplinary interventions are provided to patients with CKD, no established systems for successful treatment and care exist. Therefore, in this nationwide multicenter cohort study, we analyzed the results of our investigation into the impact of multidisciplinary care systems on CKD patients. Moreover, we investigated the optimal number of healthcare professionals that make up a multidisciplinary care team for maintaining kidney function and improving prognosis.

Methods

The Ethics Committee of Nihon University Itabashi Hospital approved the study (No. RK-220412-10), which was conducted according to the 2015 Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor, and Welfare and Japanese privacy laws. All procedures were performed based on the Helsinki Declaration. The use of de-identified data allowed the requirement for informed consent to be omitted. The registration number of the study in the University Hospital Medical Information Network is UMIN000049995.

Study design and participants

Approximately 3,000 Japanese patients who were enrolled at 24 chosen medical institutions in Japan, which play a key role in the treatment of CKD patients in each area, were included in this nationwide multicenter study, which was conducted by the committee for the evaluation and dissemination of CKDE in the JKA. The study was intended to reflect the treatment methods used by most Japanese people. A total of 19 tertiary hospitals and five secondary hospitals were included. Patients with CKD who received continuous multidisciplinary care and had data on kidney function available for the 12 months before and the 24 months after receiving multidisciplinary care in Japan were tracked through the end of 2021, and the study period covered January 2015 to December 2019. Patients with CKD who had at least one visit to a nephrologist and were examined by a nephrologist to require more intensive treatment with a multidisciplinary intervention were eligible. The following criteria were used to exclude participants: age younger than 20 years; CKD stages 1 and 2, i.e., ≥60 mL/min/ 1.73 m^2 for estimated glomerular filtration rate (eGFR); acute kidney injury; active malignant disease; transplant recipient; history of long-term dialysis; received multidisciplinary care in the past; and missing data on age, sex, or kidney function. According to the number of healthcare professionals on the multidisciplinary care team, the patients were divided into groups A, B, C, and D. The patients in group A were defined as patients who received multidisciplinary medical care from nephrologists and another professional, either nurses or registered dieticians. Patients in group B were defined as patients who received multidisciplinary medical care from three professionals, such as nurses and registered dieticians, besides nephrologists. Patients in group C were defined as patients who received multidisciplinary medical care from four professionals, such as nurses, registered dieticians, and pharmacists, besides nephrologists. Patients in group D were defined as those who received multidisciplinary medical care from five or more professionals, including nurses, registered dieticians, pharmacists, physical therapists, clinical laboratory technicians, and social workers, besides nephrologists. The patients were further separated into two subgroups based on whether they had diabetes or not. The quality of the educational content, which included medical management, dietary recommendations, and lifestyle changes, provided was maintained according to the most recent CKD treatment manual or CKD Teaching Guidebook for CKDEs published by the JKA [9,10]. Physical therapists guide exercise therapy to prevent frailty and sarcopenia, according to the Guideline for the Japanese Society of Renal Rehabilitation (JSRR) [11]. Clinical laboratory technicians explain the target values and significance of kidney-related inspection items to patients with all stages of CKD. Social workers provide patients and families with information on available care services and social resources.

Data collection

The demographic and clinical parameters of the patients, such as their age, sex, history of CVD, primary cause of CKD, and body mass index (BMI), were recorded, as well as hemoglobin, creatinine (Cr), urinary protein, serum albumin, urea nitrogen, eGFR, and glycated hemoglobin (HbA1c) for diabetes patients at baseline. CVD was defined as hemorrhagic stroke, limb amputation, coronary artery disease, and ischemic stroke. For Japanese patients, the following formula was used to determine the eGFR: eGFR (mL/min/1.73 m^2) = 194 × serum Cr$^{-1.094}$ × age$^{-0.287}$ (×0.739 for female) [12]. The eGFR values were obtained at 12 months before the intervention by multidisciplinary care and at 6 months, 1 year, and 2 years after the intervention. The annual change in the eGFR (mL/min/1.73 m^2/year) was calculated at each time point of measurement using the following four formulas:

(1) [eGFR (baseline) – eGFR (at 12 months before multidisciplinary care)];
(2) [eGFR (at 6 months after multidisciplinary care) – eGFR (baseline)] × 2;
(3) [eGFR (at 12 months after multidisciplinary care) – eGFR (baseline)]; and
(4) [eGFR (at 24 months after multidisciplinary care) – eGFR (baseline)] × 1/2.

Urinary protein was calculated as the ratio of urinary protein to creatinine (UPCR). The UPCR values were measured at the start of the intervention and at intervals of 6, 12, and 24 months. Method and place of intervention (outpatient or inpatient), number or duration of the intervention (number of visits for intervention for outpatients or hospitalization days for inpatients), and type and number of professionals were collected. The frequency of intervention in outpatient settings, only visits for multidisciplinary care were counted, not every facility visit. Composite outcomes, including dates of all-cause death or the initiation of RRT, were recorded until the composite endpoint was reached or the end of 2021, whichever came earlier. Furthermore, types of RRT, which are hemodialysis, peritoneal dialysis, or kidney transplantation, were recorded.

Statistical analysis

The number and proportion of the data, the mean and standard deviation, or the median (interquartile range [IQR]) are presented. The intragroup comparison was analyzed using two-tailed paired t tests. The chi-squared test was used to analyze categorical variables, and the t test was used to evaluate continuous variables. The repeated-measures analysis of variance was used to compare four groups, with the appropriate use of the Kruskal-Wallis or Tukey's honestly significant difference tests. The log-rank test was used to evaluate the composite endpoint between groups after the Kaplan-Meier technique was used to estimate it. There were both univariate and multivariate analyses using Cox proportional hazards models adjusted for confounders to examine associations between the number of specialists in multidisciplinary intervention and the composite outcome during 7 years of follow-up. Age, sex, CVD history, and presence or absence of diabetes were considered when calculating the hazard ratios (HRs) using model 1. In addition to the variables in model 1, eGFR and UPCR levels at baseline were considered when calculating the HRs using model 2. In addition to the variables in model 2, model 3 was adjusted for baseline BMI, serum albumin, and hemoglobin levels. Furthermore, based on whether a subject had diabetes or not, subgroup analysis was performed. Additionally, subgroup analysis was performed to evaluate the composite endpoint as per CKD stages at baseline in each group, four groups in each CKD stage at baseline, and according to different intervention settings, i.e., inpatient-based or outpatient-based. HRs with 95% confidence intervals (CIs) and p-values are used to express the model results. For the regression analyses, the imputation of missing data was performed using conventional methods, as necessary. JMP version 13.0 (SAS Institute Inc.) was utilized for all analyses. Statistics were deemed significant at a p-value of <0.05.

Results

Patient features at the multidisciplinary care initiation

Overall, 3,296 patients were enrolled in this study, but only 2,957 were eligible to proceed after 339 were discarded (Fig. 1). Table 1 displays the patient characteristics at the start of multidisciplinary care. Of the patients, 74.1% were male, with a mean age of 70.5 ± 11.6 years. UPCR level was 1.09 g/gCr (0.23–2.98 g/gCr), and the mean eGFR level was 25.8 ± 12.5 mL/min/1.73 m^2. Diabetic kidney disease (42.9%) was the most common primary disease of CKD, followed by hypertensive nephropathy (33.0%) and chronic glomerulonephritis (13.4%). In terms of CKD stages, the most frequent stage was G4 (42.3%), followed by G3b (26.1%) and G5 (21.9%). The average number of professionals on the multidisciplinary care team, including nephrologists, was 3.8 ± 1.2, and it differed significantly between secondary hospitals and tertiary hospitals, 4.3 ± 0.6 and 3.5 ± 1.2,

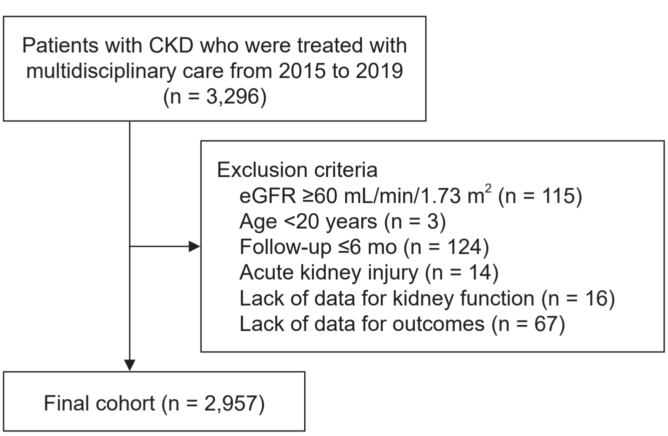


Figure 1. Flowchart of study participants.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 1. All participants' baseline data

Variable	Value
No. of patients	2,957
Male sex	2,192 (74.1)
Age (yr)	70.5 ± 11.6
Body mass index (kg/m^2)	24.2 ± 4.3
Serum Cr (mg/dL)	2.43 ± 1.29
eGFR (mL/min/1.73 m^2)	25.8 ± 12.5
Annual decline of eGFR (mL/min/1.73 m^2/yr)	−5.9 ± 7.2
Serum urea nitrogen (mg/dL)	31 (23–43)
Hemoglobin (g/dL)	11.7 ± 1.9
Serum albumin (g/dL)	3.8 ± 0.5
Urinary protein (g/gCr)	1.09 (0.23–2.98)
Comorbidity of CVD	846 (28.6)
Comorbidity of diabetes	1,432 (48.4)
Glycated hemoglobin (for diabetes)	6.4 ± 1.0
Primary cause of CKD	
Diabetic kidney disease	1,269 (42.9)
Hypertensive nephropathy	975 (33.0)
Chronic glomerulonephritis	397 (13.4)
PCKD	87 (2.9)
Others	229 (7.8)
CKD stage	
G3 (G3a + G3b)	1,060 (35.8)
G3a	288 (9.7)
G3b	772 (26.1)
G4	1,251 (42.3)
G5	646 (21.9)
No. of professionals of MDC team	3.8 ± 1.2
2	656 (22.2)
3	398 (13.5)
4	902 (30.5)
5	976 (33.0)
6	22 (0.8)
Membership of MDC team	
Nurses	2,545 (86.2)
Registered dieticians	2,703 (91.5)
Pharmacists	1,885 (63.8)
Physical therapists	772 (26.1)
Clinical laboratory technicians	171 (5.8)
Social workers	68 (2.3)
Others	24 (0.8)

Data are expressed as number only, number (%), mean ± standard deviation, or median (interquartile range).
CKD, chronic kidney disease; Cr, creatinine; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDC, multidisciplinary care; PCKD, polycystic kidney disease.

respectively (p < 0.0001). The number of multidisciplinary care team members comprising five professionals was most common (33.0%), followed by four (30.5%) and two (22.2%). Most of the multidisciplinary care team members were registered dieticians (91.5%), followed by specific nurses (86.2%), pharmacists (63.8%), and physical therapists (26.1%).

The baseline patient characteristics were compared between the four groups based on the number of members of the multidisciplinary care team. Table 2 compares the baseline characteristics of the patients in the four groups according to the number of multidisciplinary care providers. Male dominance, outpatient settings, higher levels of urinary protein and serum albumin, and a higher rate of diabetic kidney disease characterized groups A and B. Regarding kidney function severity, group A had the lowest eGFR levels at baseline and included the highest rate of stage G5. Conversely, groups C and D were characterized with higher rate of female patients, inpatient settings, lower urinary protein levels, and a higher rate of hypertensive nephropathy and stage G3.

Table 3 shows the details of the membership of the

Table 2. Comparison of patient's characteristics according to the number of the multidisciplinary care team

Variable	Group A	Group B	Group C	Group D	p-value
No. of patients	658	399	902	998	<0.0001
Male sex	481 (73.1)	371 (92.9)	630 (69.9)	710 (71.1)	
Age (yr)	69.2 ± 12.5	71.2 ± 10.6	69.9 ± 12.1	71.9 ± 10.8	<0.0001
Place of intervention					<0.0001
Outpatient	641 (97.4)	366 (91.7)	178 (19.7)	8 (0.8)	
Inpatient	17 (2.6)	33 (8.3)	724 (80.3)	990 (99.2)	
Body mass index (kg/m^2)	23.7 ± 4.1	23.4 ± 3.5	24.5 ± 4.6	24.4 ± 4.2	<0.0001
Serum Cr at baseline (mg/dL)	2.57 ± 1.38	2.30 ± 1.07	2.46 ± 1.36	2.26 ± 1.17	<0.0001
eGFR before 12 mo (mL/min/1.73 m^2)	31.6 ± 15.2	34.4 ± 14.1	34.1 ± 15.8	32.9 ± 12.7	0.13
eGFR at baseline (mL/min/1.73 m^2)	24.8 ± 13.0	26.5 ± 12.2	26.1 ± 12.9	27.1 ± 12.2	0.004
Serum urea nitrogen (mg/dL)	34 (24–49)	31 (24–41)	31 (3–44)	30 (23–41)	<0.0001
Hemoglobin (g/dL)	11.7 ± 1.8	11.7 ± 1.9	11.8 ± 2.0	11.7 ± 1.9	0.39
Serum albumin (g/dL)	3.8 ± 0.5	3.8 ± 0.5	3.7 ± 0.6	3.7 ± 0.5	0.008
Urinary protein (g/gCr)	1.30 (0.35–3.20)	1.39 (0.25–3.34)	1.16 (0.26–3.43)	0.86 (0.17–2.43)	0.048
Comorbidity of CVD	203 (30.9)	91 (22.8)	220 (24.4)	333 (33.4)	<0.0001
Comorbidity of diabetes	319 (48.5)	258 (64.7)	352 (39.0)	503 (50.4)	<0.0001
Glycated hemoglobin (for diabetes)	6.4 ± 1.0	6.3 ± 0.8	6.5 ± 1.1	6.4 ± 1.1	0.009
Primary cause of CKD					<0.0001
Diabetic kidney disease	300 (45.7)	234 (58.5)	301 (33.4)	434 (43.5)	
Hypertensive nephropathy	164 (24.8)	96 (24.4)	361 (40.0)	354 (35.5)	
Chronic glomerulonephritis	101 (15.4)	37 (9.0)	133 (14.8)	126 (12.6)	
PCKD	18 (2.7)	25 (6.3)	31 (3.4)	13 (1.3)	
Others	75 (11.4)	7 (1.8)	76 (8.4)	71 (7.1)	
CKD stage					<0.0001
G3 (G3a + G3b)	215 (32.8)	141 (35.2)	332 (36.8)	372 (37.3)	
G3a	68 (10.4)	33 (8.3)	97 (10.7)	90 (9.0)	
G3b	147 (22.4)	108 (26.9)	235 (26.1)	282 (28.3)	
G4	263 (40.0)	177 (44.7)	356 (39.5)	455 (45.6)	
G5	180 (27.2)	81 (20.1)	214 (23.7)	171 (17.1)	
All-cause death	30 (4.6)	16 (4.0)	44 (4.9)	38 (3.8)	0.66
Initiation of RRT	172 (28.4)	73 (19.1)	240 (28.5)	159 (16.9)	<0.0001

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range).
Cr, creatinine; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PCKD, polycystic kidney disease; RRT, renal replacement therapy.

Table 3. Healthcare professionals of the MDC teams in the four groups

Variable	Group A	Group B	Group C	Group D	p-value
No. of patients	658	399	902	998	-
Membership of MDC team					
Nurses	248 (37.7)	399 (100)	902 (100)	998 (100)	<0.0001
Registered dieticians	410 (62.3)	395 (99.5)	901 (99.9)	998 (100)	<0.0001
Pharmacists	0 (0)	0 (0)	889 (98.6)	996 (99.8)	<0.0001
Physical therapists	0 (0)	0 (0)	1 (0.1)	771 (77.3)	<0.0001
Clinical laboratory technicians	0 (0)	0 (0)	0 (0)	171 (17.1)	<0.0001
Social workers	0 (0)	0 (0)	1 (0.1)	67 (6.7)	<0.0001
Others	0 (0)	2 (0.5)	12 (1.3)	10 (1.0)	0.03

Data are expressed as number (%).
MDC, multidisciplinary care.

multidisciplinary care team in the four groups. group A was composed of nephrologists and specific nurses or registered dieticians. Group B was mostly composed of nephrologists, nurses, and registered dieticians (99.5%). Group C was mostly composed of nephrologists, nurses, registered dieticians, and pharmacists (98.6%). Group D included physical therapists, clinical laboratory technicians, and social workers, besides nephrologists, nurses, registered dieticians, and pharmacists. Most of the nurses and registered dieticians were included in groups B, C, and D, whereas pharmacists were included in groups C and D. Frequency of multidisciplinary care for outpatient was 9.1 ± 4.5 times and duration of hospital stay for inpatient were 7 days (5–12 days).

Changes in Δestimated glomerular filtration rate and urinary protein to creatinine levels before and after multidisciplinary care in the four groups

The mean annual decline in eGFR (ΔeGFR) was significantly improved from –5.89 ± 7.17 mL/min/1.73 m^2/year before multidisciplinary intervention to –0.44 ± 5.21 mL/min/1.73 m^2/year at 6 months, –1.52 ± 6.09 mL/min/1.73 m^2/year at 12 months, and –1.48 ± 3.78 mL/min/1.73 m^2/year at 24 months after intervention (for all of them, $p < 0.0001$) (Supplementary Fig. 1, available online). As shown in Fig. 2, the mean ΔeGFR was significantly improved from before the multidisciplinary intervention to all time points after intervention in all groups. The mean ΔeGFR before intervention (ΔeGFR [–1 year]) in groups B and C was –6.50 ± 6.24 mL/min/1.73 m^2/year, and –6.61 ± 7.97 mL/min/1.73 m^2/year, respectively, and a significant difference existed between the groups (p = 0.005) (Supplementary Table 1, available online). However, the ΔeGFR values for the four groups did not significantly differ after 6, 12, or 24 months, following the intervention.

The median UPCR level was significantly decreased from 1.09 g/gCr (0.23–2.98 g/gCr) at baseline to 1.00 g/gCr (0.24–2.71 g/gCr) at 6 months, 0.89 g/gCr (0.21–2.38 g/gCr) at 12 months, and 0.82 g/gCr (0.20–2.22 g/gCr) at 24 months ($p < 0.0001$ for all of them) (Supplementary Fig. 2, available online). Fig. 3A shows that the median UPCR levels in group A significantly decreased from baseline to 6 and 12 months after the intervention. Conversely, the UPCR levels in groups B, C, and D significantly decreased from baseline at all time points after intervention (Fig. 3B–D). The four groups had significantly different median UPCR levels at baseline, and this difference persisted for 24 months after the intervention (Supplementary Table 2, available online).

Outcomes

The median observation period was 36 months (IQR, 22–52 months), during which 128 patients (4.3%) died, 649 (22.0%) initiated RRT, and 59 (2.0%) were lost to follow-up; 2,121 patients (71.7%) of all patients were alive without RRT. RRT consisted of hemodialysis in 527 patients (81.2%), peritoneal dialysis in 61 (9.4%), and kidney transplantation in 23 patients (3.5%).

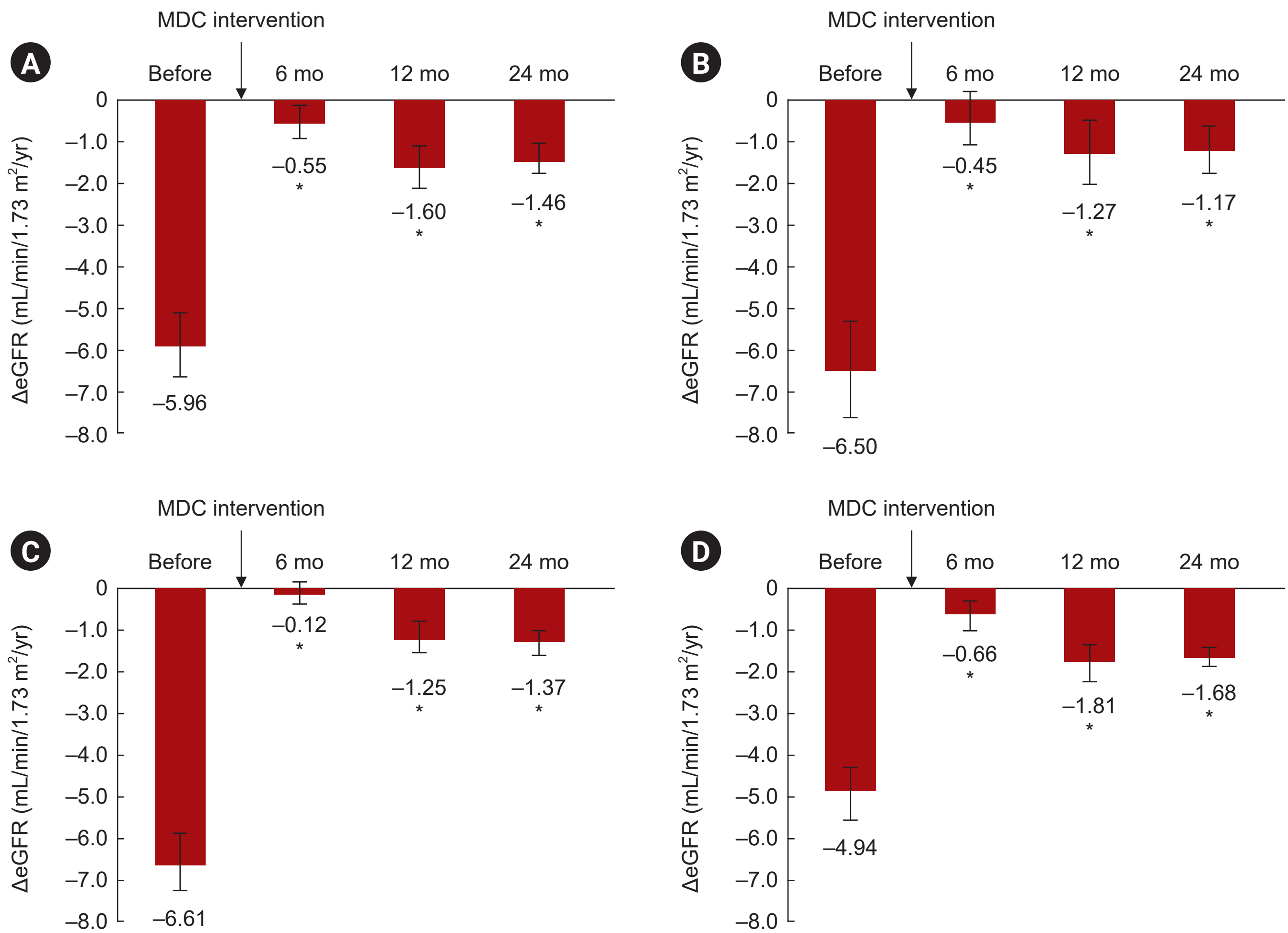


Figure 2. Annual changes in eGFR decline (ΔeGFR) in the 12 months before and 24 months after initiation of MDC. (A) Group A, (B) group B, (C) group C, and (D) group D. Data are shown as the mean. Bars indicate the 95% confidence interval. *$p < 0.0001$ vs. before the start of MDC.
eGFR, estimated glomerular filtration rate; MDC, multidisciplinary care.

Comparison of composite endpoints between the four groups

There was a significant difference between the four groups according to the Kaplan-Meier analysis for the composite endpoint (all-cause mortality and the start of RRT; $p < 0.0001$, log-rank test) (Fig. 4). Compared with group A (reference), the unadjusted HR for group D was significantly lower, at 0.60 (95% CI, 0.49–0.74; $p < 0.0001$) (Table 4). When background characteristics including age, sex, CVD history, and whether or not one has diabetes have been taken into account (model 1), a significantly decreased HR of 0.57 (95% CI, 0.47–0.71; $p < 0.0001$) was observed in group D. After adjusting for baseline eGFR and UPCR levels in addition to the components in model 1 (model 2), group D had a significantly lower HR of 0.57 (95% CI, 0.46–0.70; $p < 0.0001$). Following another adjustment for BMI, serum albumin, and hemoglobin levels at baseline in addition to factors of model 2, group D had a significantly lower HR (0.60; 95% CI, 0.48–0.73; $p < 0.0001$).

Subgroup analysis of the four groups based on whether they had diabetes or not

The patients were split into two groups based on whether they had diabetes or not. The composite endpoint for dia-

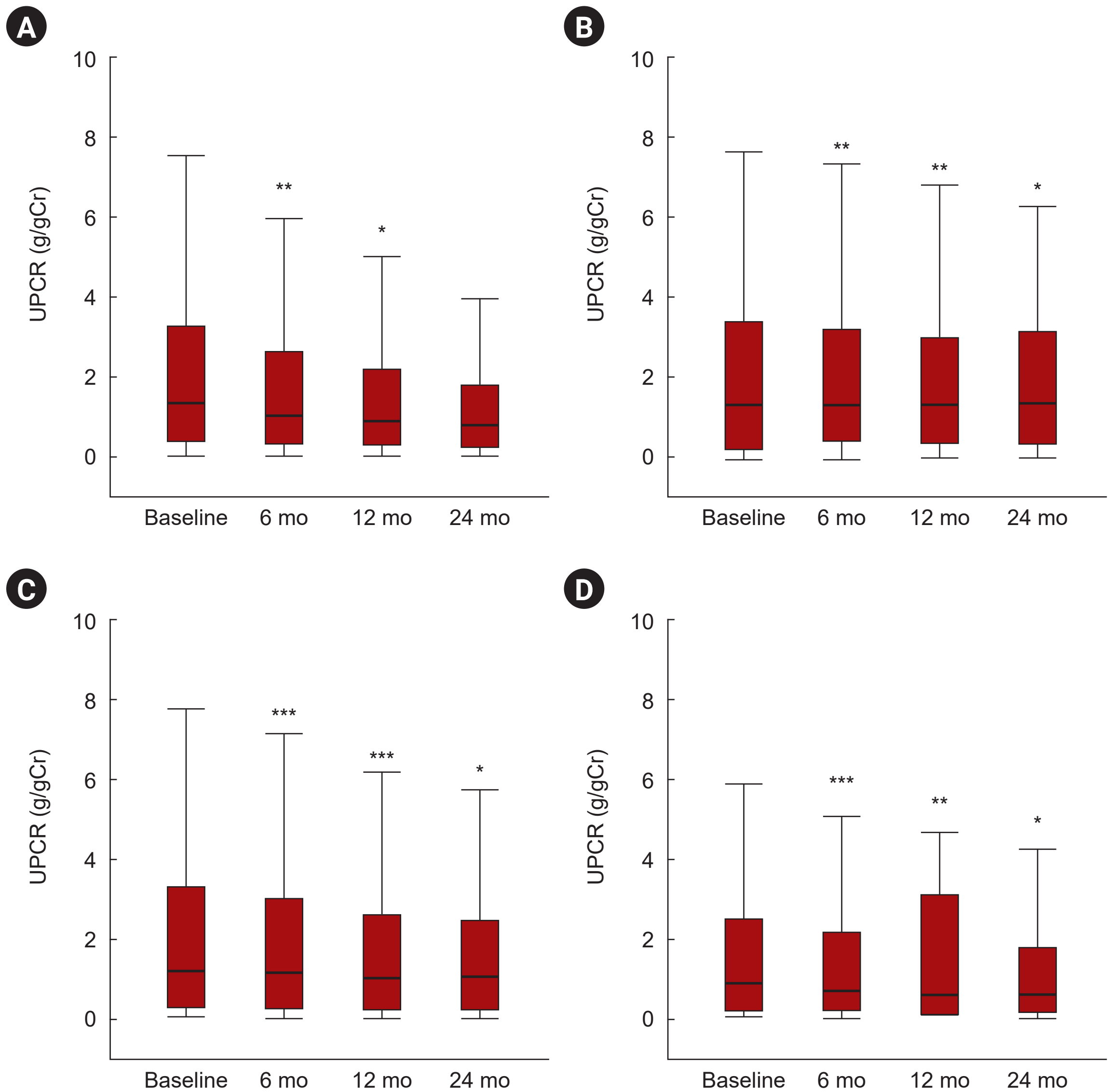
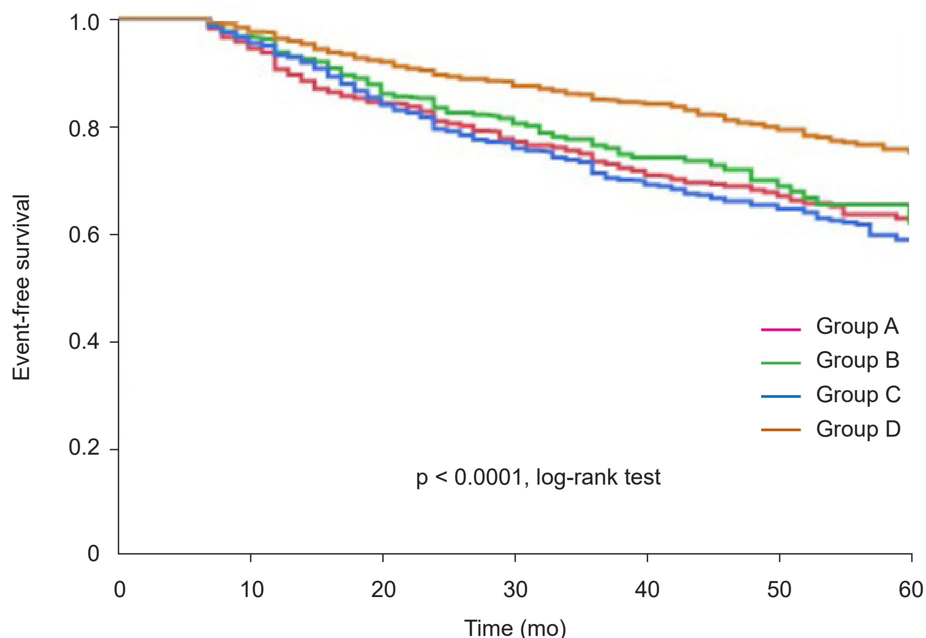


Figure 3. Changes in urinary protein levels between the time of initiation of MDC and 24 months after initiation of MDC. (A) Group A, (B) group B, (C) group C, and (D) group D. Data are shown as the median and interquartile range. ***p < 0.0001, **p < 0.001, *p < 0.01 vs. baseline.
MDC, multidisciplinary care; UPCR, urinary protein to creatinine ratio.

betes patients differed significantly across the four groups according to Kaplan-Meier analysis ($p < 0.0001$, log-rank test) (Fig. 5A). Cox proportional analysis revealed the unadjusted HR for the composite endpoint. Compared to that in group A (reference), the HRs in groups B and D were noticeably lower, which were at 0.70 (95% CI, 0.51–0.95; p = 0.02) and 0.59 (95% CI, 0.46–0.77; p < 0.0001) (Table 5). Once background variables including sex, age, and CVD history have been taken into account (model 1), the HRs in groups B and D were 0.72 (95% CI, 0.52–0.98; p = 0.04) and 0.60 (95% CI, 0.46–0.78; p = 0.0001), respectively. Another adjustment for HbA1c, eGFR, and UPCR level at baseline in addition to the factors of model 1 (model 2), the HR in groups B and D were 0.69 (95% CI, 0.49–0.97; p = 0.03) and 0.57 (95% CI, 0.43–0.76; p = 0.0002), respectively. After further adjustment for BMI, serum albumin, and hemoglobin



Numbers at risk

Group A	656	617	496	371	273	171	79
Group B	403	390	298	239	122	67	34
Group C	902	861	700	554	405	291	162
Group D	998	977	831	699	485	309	157

Figure 4. Japanese chronic kidney disease patients' Kaplan-Meier curves for the occurrence of all-cause mortality and the start of renal replacement therapy in four groups according to the number of professionals consisting of the multidisciplinary care team. Group A vs. group B, $p = 0.30$; group A vs. group C, $p = 0.41$; group A vs. group D, $p < 0.0001$; group B vs. group C, $p = 0.054$; group B vs. group D, $p < 0.0001$; group C vs. group D, $p < 0.0001$.

levels at baseline in addition to the factors of model 2, only group D had a significantly lower HR of 0.55 (95% CI, 0.41–0.75; p = 0.0002).

In patients with no diabetes, Kaplan-Meier analysis for the composite endpoint revealed a significant difference between all four groups (p < 0.0001, log-rank test) (Fig. 5B). Group D had a considerably lower unadjusted HR for the composite endpoint than group A (reference) (0.54; 95% CI, 0.39–0.74; p = 0.0001). The HR in group D was 0.53 (95% CI, 0.40–0.73; p = 0.0001) after background characteristics, including age, sex, and a history of CVD, were adjusted (model 1). After further adjustment for eGFR and UPCR levels at baseline in addition to the factors of model 1 (model 2), the HR in group D was 0.70 (95% CI, 0.51–0.98; p = 0.04). After further adjustment for BMI, serum albumin, and hemoglobin levels at baseline in addition to factors of model 2, group D had a significantly lower HR of 0.68 (95% CI, 0.48–0.96; p = 0.03) as shown in Table 6.

Subgroup analysis based on chronic kidney disease stages at baseline in each group, four groups in each chronic kidney disease stage, and the inpatient or outpatient setting

All-cause mortality and the RRT initiation rate depended on the disease stage in all groups. Substantial differences (all p < 0.0001, log-rank test) were found in the composite endpoint as per the CKD stage at baseline in each group (Supplementary Fig. 3, available online). There was a significant difference between the four groups in only stage G4 according to the Kaplan-Meier analysis for the composite endpoint (all-cause mortality and the start of RRT; p < 0.0001, log-rank test) (Supplementary Fig. 4, available online). There was no significant difference between the four groups in other CKD stages.

Table 4. In patients with chronic kidney disease, Cox proportional hazards models adjusted for confounding factors were used to compare the groups according to the number of professionals, all-cause mortality, and the start of renal replacement therapy

Group	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
A	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
B	0.88 (0.69–1.12)	0.30	0.78 (0.61–1.00)	0.05	0.89 (0.68–1.15)	0.37	0.81 (0.87–1.29)	0.13
C	1.08 (0.89–1.31)	0.41	1.15 (0.95–1.40)	0.16	1.17 (0.95–1.45)	0.13	1.06 (0.87–1.29)	0.51
D	0.60 (0.49–0.74)	<0.0001	0.57 (0.47–0.71)	<0.0001	0.57 (0.46–0.70)	<0.0001	0.60 (0.48–0.73)	<0.0001

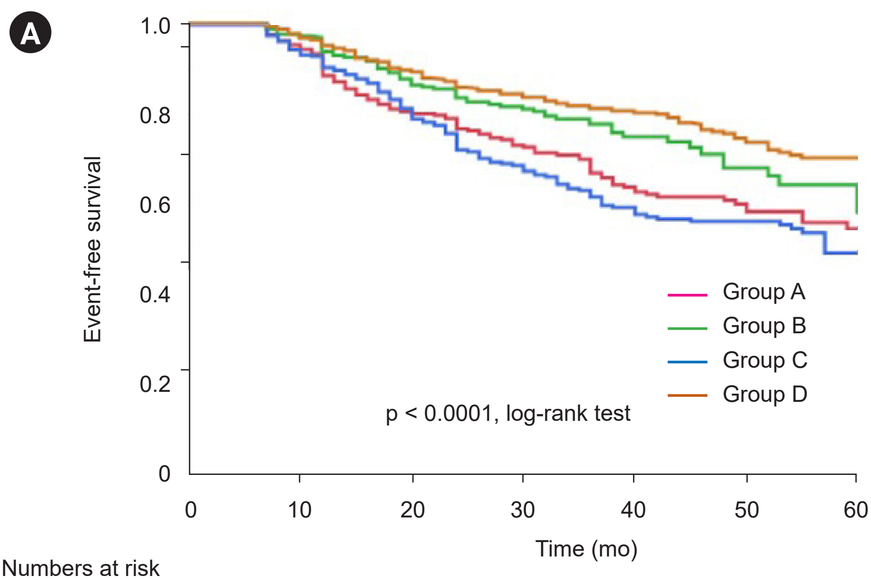
Age, sex, cardiovascular disease history, and the presence or absence of diabetes mellitus were all basic characteristics that were adjusted for in model 1. Model 2 was adjusted for estimated glomerular filtration rate and urinary protein levels at baseline in addition to factors of model 1. Model 3 was adjusted for body mass index, serum albumin, and hemoglobin levels at baseline in addition to factors of model 2.
Nephrologists in group A plus one professional; nephrologists in group B plus two professionals; nephrologists in group C plus three professionals; and nephrologists in group D plus four or more professionals.
CI, confidence interval; HR, hazard ratio.

The setting of multidisciplinary care was different between groups A, B and groups C, D. Subgroup analysis was conducted according to outpatient and inpatient settings. Composite endpoint was compared between groups A and B in outpatient setting (Supplementary Fig. 5A, available online), and between groups C and D in inpatient setting (Supplementary Fig. 5B, available online). Although there was no significant difference in groups A and B in outpatient setting (Supplementary Table 3, available online), group D showed significantly lower HR of 0.56 (95% CI, 0.45–0.69; $p < 0.0001$) compared with group C (reference) after adjusted for all confounders in inpatient setting (Supplementary Table 4, available online).

Discussion

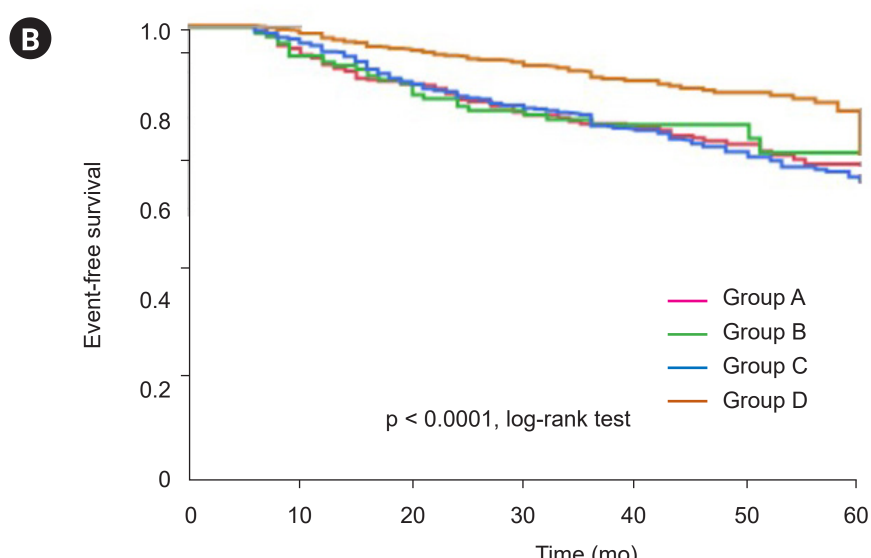
Our nationwide cohort study demonstrated that the multidisciplinary care conducted by nephrologists with at least another specialist could prevent the decline of eGFR and reduce proteinuria levels for 2 years after multidisciplinary care. Furthermore, the multifactorial intervention provided by a team comprised of five or more professionals, including nephrologists, has been shown to improve patient outcomes for 7 years. The present study included 2,957 individuals from 24 facilities in Japan; therefore, the large sample size drawn from a multicenter study is one of its main advantages, along with the relatively long observation and the inclusion of a comparatively high number of elderly patients. This study is the first to indicate that a multidisciplinary care team with five or more professionals may be able to prevent initiating RRT and reduce all-cause mortality regardless of whether the CKD patients have diabetes or not. A multidisciplinary care team should include a nephrologist and other professionals from other fields and is recommended for those with stages 3 to 5 of CKD.

The mean annual decline of eGFR before multidisciplinary care was –5.9 mL/min/1.73 m^2 in this study. It has been reported that when the eGFR falls below 45 mL/min/1.73 m^2, it declines at a rate of –9.9 mL/min/1.73 m^2/year in diabetic nephropathy and –4.8 mL/min/1.73 m^2/year in hypertensive nephropathy until the initiation of dialysis in Japanese CKD patients [13]. Furthermore, the annual decline rate of eGFR from 45 mL/min/1.73 m^2 to dialysis initiation was greater than the decline rate of eGFR from 60 mL/min/1.73 m^2 to 45 mL/min/1.73 m^2 [13]. Therefore, annual decline of eGFR was higher in the present study because the mean eGFR levels at baseline was 25.8 ± 12.5 mL/min/1.73 m^2. According to reports, poor drug adherence has been linked to problems, CKD progression, unplanned hospitalization, higher medical expenses, early impairment, and mortality [14,15]. Across disease states, treatment protocols, and age groups, men have relatively high discontinuous visit rates; the first few months of treatment are when this rate is highest [16]. Most patients with CKD, particularly those in stage 3, are asymptomatic, and interruption of visits is one of their significant issues. Reportedly, multidisciplinary care improves adherence to management targets given in CKD guidelines, and this adherence leads to an enhanced renal prognosis even in patients with CKD stage G3 [17]. Collaborative integration by multidisciplinary care professionals is critical in helping patients modify their lifestyles and efficiently achieve



Numbers at risk

	0	10	20	30	40	50	60
Group A	319	296	230	172	118	70	33
Group B	258	250	197	157	77	45	23
Group C	352	327	260	188	128	99	52
Group D	503	487	406	336	245	153	76



Numbers at risk

	0	10	20	30	40	50	60
Group A	339	323	268	201	156	102	47
Group B	141	136	106	82	46	26	15
Group C	550	534	440	366	272	192	110
Group D	495	490	425	363	240	156	81

Figure 5. Kaplan-Meier curves for the incidence of all-cause death and the start of renal replacement therapy in these patients. Japanese chronic kidney disease patients with (A) and without (B) diabetes are divided into four groups based on the number of professionals who make up the multidisciplinary care team. (A) Group A vs. group B, $p = 0.002$; group A vs. group C, $p = 0.78$; group A vs. group D, $p < 0.0001$; group B vs. group C, $p = 0.0004$; group B vs. group D, $p = 0.69$; group C vs. group D, $p < 0.0001$. (B) Group A vs. group B, $p = 0.70$; group A vs. group C, $p = 0.82$; group A vs. group D, $p = 0.0001$; group B vs. group C, $p = 0.80$; group B vs. group D, $p = 0.02$; group C vs. group D, $p < 0.0001$.

Table 5. Diabetes patients with chronic kidney disease are compared between the four groups for all-cause mortality and the start of renal replacement therapy using Cox proportional hazards models adjusted for confounding variables

Group	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
A	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
B	0.70 (0.51–0.95)	0.02	0.72 (0.52–0.98)	0.04	0.69 (0.49–0.97)	0.03	1.13 (0.87–1.46)	0.34
C	1.04 (0.81–1.32)	0.78	1.06 (0.83–1.35)	0.67	1.06 (0.80–1.41)	0.66	0.88 (0.70–1.12)	0.30
D	0.59 (0.46–0.77)	<0.0001	0.60 (0.46–0.78)	0.0001	0.57 (0.43–0.76)	0.0002	0.55 (0.41–0.75)	0.0002

Age, sex, and cardiovascular disease history were all basic characteristics that were adjusted for in model 1. Model 2 was adjusted for estimated glomerular filtration rate and urinary protein levels at baseline in addition to factors of model 1. Model 3 was adjusted for body mass index, serum albumin, and hemoglobin levels at baseline in addition to factors of model 2.
Nephrologists in group a plus one other professional; nephrologists in group B plus two other professionals; nephrologists in group C plus three other professionals; nephrologists in group D plus four or more other professionals.
CI, confidence interval; HR, hazard ratio.

Table 6. Comparison of the all-cause mortality and the start of renal replacement therapy in patients without diabetes but with chronic kidney disease between the four groups using Cox proportional hazards models adjusted for confounding factors

Group	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
A	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
B	0.92 (0.59–1.38)	0.70	0.95 (0.61–1.45)	0.83	1.32 (0.83–1.05)	0.24	1.25 (0.72–2.07)	0.41
C	0.97 (0.74–1.28)	0.82	1.03 (0.78–1.35)	0.86	1.15 (0.86–1.55)	0.35	1.06 (0.78–1.46)	0.71
D	0.54 (0.39–0.74)	0.0001	0.53 (0.40–0.73)	0.0001	0.70 (0.51–0.98)	0.04	0.68 (0.48–0.96)	0.03

Age, sex, and cardiovascular disease history were all basic characteristics that were adjusted for in model 1. Model 2 was adjusted for estimated glomerular filtration rate and urinary protein levels at baseline in addition to factors of model 2. Model 3 was adjusted for body mass index, serum albumin, and hemoglobin levels at baseline in addition to factors of model 2.
Nephrologists in group A plus one other professional; nephrologists in group B plus two other professionals; nephrologists in group C plus three other professionals; nephrologists in group D plus four or more other professionals.
CI, confidence interval; HR, hazard ratio.

treatment goals established by guidelines [18]. Although the present study included 2,957 patients, only 2% of follow-up on some patients was lost. However, we could not evaluate whether the multidisciplinary care in this study was able to successfully achieve behavioral modification, improve patient compliance and adherence, and reduce the discontinuation rate of outpatient visits. Nevertheless, we believe that multidisciplinary care may be associated with improved patient health literacy and the prevention of worsening kidney function.

Nephrologists, dieticians, nurses, pharmacists, and social workers generally make up the multidisciplinary care team for patients with CKD, and each of them is crucial to the management of these patients [8]. However, the present study found that the composition of professionals in the multidisciplinary care team varied significantly by institution and intervention method. Regarding intervention methods, multidisciplinary care teams consisting of two or three professionals, including nephrologists, were primarily delivered in outpatient settings, whereas teams of four or more professionals were delivered in the inpatient setting. Inpatient multidisciplinary care programs for patients with CKD have not been implemented extensively in Western countries, probably reflecting differences in the medical insurance system between Japan and Western countries. Although multidisciplinary care provided in an outpatient setting is reimbursed for patients with diabetic kidney disease in Japan, it is not reimbursed for patients with other etiologies of CKD. However, full reimbursement is available for these patients if they are admitted to hospital. Accordingly, interventions by pharmacists and physical therapists are possible in the inpatient setting. Moreover, regarding the number of healthcare professionals consisting of multidisciplinary care teams, registered dieticians are the most common, followed by specific nurses, pharmacists, physical therapists, and the number of physical therapists is greater than that of social workers in Japan. As per recent studies, kidney function is linked to physical activity in people with CKD, and increasing physical activity levels may slow the decline of kidney function [19–22]. There is a guideline for exercise therapy for patients with predialysis CKD and dialysis from the JSRR [11]. Consequently, physical therapists, preferably with CKD knowledge, were widely used to treat CKD patients in Japan, and they must be considered members of multidisciplinary care teams. Our results showed that the most physical therapists were included in group D. Therefore, further investigation would be needed since the physical therapists might be a key player in improving the prognosis of patients with CKD. According to a meta-analysis, CKD patients receiving multidisciplinary care had a considerably lower chance of dying from any cause than those who were not receiving it [23]. However, when nephrologists and nurses made up the multidisciplinary care teams, there was no significant difference in all-cause mortality between the multidisciplinary and non-multidisciplinary care groups. Furthermore, it has been hypothesized that the all-cause death rate for CKD patients would decrease when the multidisciplinary care team included not just nephrologists and nurses but also experts from other specialties. A multidisciplinary care team that only includes nephrologists and nurses might not be the best choice for improving outcomes for CKD patients according to a meta-analysis [23]. The present study found that the intervention of at least one professional besides nephrologists can prevent the decline of kidney function in CKD patients more than nephrologists alone. Moreover, the present study revealed that a multidisciplinary care team consisting of five or more healthcare professionals could provide the best outcomes, regardless of any underlying CKD disease. However, further investigations are needed to determine which professionals and how many staff members comprise multidisciplinary care teams that achieve the best outcomes.

A self-management program's overarching objective is to empower and enable people to advance their knowledge and abilities in self-management [24]. Therefore, it helps diabetes patients lower their risk of developing long-term microvascular and macrovascular problems, severe hypoglycemia, and diabetic ketoacidosis. Besides maximizing patient well-being, self-management programs seek to enhance the quality of life and achieve treatment satisfaction [25]. Patients with diabetes are frequently given lifestyle management services, such as medical nutrition therapy, physical exercise, weight loss counseling, smoking cessation counseling, and emotional support. Fundamental components of diabetes care include self-management training and assistance. According to reports, patients with diabetes who participate in a program with a planned, patient-centered curriculum and more than 10 hours of contact time each week have the best results [26]. Self-management education, according to the American Diabetes Association, is a continuous process that encourages the information, skills, and competencies required for diabetes self-care. It also combines a patient-centered approach and collaborative decision making [27]. A multidisciplinary care team should deliver the program either one on one or in groups, with support available over the phone or online, according to the National Clinical Institute for Care and Excellence in the United Kingdom. This team should include at least one trained or accredited healthcare professional, such as a registered dietitian or diabetes specialist nurse [28]. A structured self-management education program should be implemented for individuals with diabetes and CKD, according to the KDIGO (Kidney Disease: Improving Global Outcome) clinical practice guideline for 2022 [29]. To provide complete treatment for patients with diabetes and CKD, policymakers and institutional decision makers promote team-based, integrated care with a focus on risk assessment and patient empowerment. Multiple factors related to lifestyle, including diet, exercise, and psychosocial factors, can influence medication noncompliance and worsen outcomes [30–32]. The present study suggested that multidisciplinary care was effective not only in diabetes patients with CKD but even in patients without diabetes but with CKD. Therefore, team-based, integrated care programs based on the structured and patient-centered curriculum should be established, and further preparation and dissemination of multidisciplinary team-based care are required for all CKD patients.

The current study has some limitations. First, we could not investigate blood pressure, body weight, laboratory findings other than kidney function, or medications, which were other unknown confounding factors. Salt restriction through multidisciplinary intervention may have lowered blood pressure, reduced proteinuria, and maintained kidney function. The patients with diabetes in group C had poor prognoses, and HbA1c level was considerably higher. Therefore, patients with higher risk factors that could not be measured or collected in this study might be included. In addition, group B had higher event rate despite ΔeGFR in group B was lower compared to group D. However, group B had higher UPCR levels through 2 years. Reduction of UPCR by multidisciplinary care might be associated with improvement of prognosis, therefore, further study should be required. Although it has been reported that an early referral to a nephrologist is more useful than a late referral, we could not collect the times and duration of management for nephrologists before multidisciplinary care. We were unable to adequately investigate the important factors involved in maintaining kidney function among the four groups. Second, the current study was excluded from a non-multidisciplinary control group. In cohort studies, multidisciplinary treatment was linked to decreased all-cause mortality, but this was not demonstrated in the randomized control trials for patients with CKD [23]. Therefore, additional prospective randomized controlled trials for patients with CKD are required to validate the efficacy of multidisciplinary therapy. Finally, there may have been some degree of patient selection and facility bias. Bias in the facility and patient selection may have existed to some extent. Although the number of professionals on the multidisciplinary care team did not vary by hospital size, it depended on the functions of each hospital, such as the type and number of healthcare professionals available. The content of the education program, the systems delivered, and the makeup of the patient population varied as per each facility. Further studies are needed to clarify whether multiple education sessions by the same personnel or one session by each personnel is superior to multidisciplinary care in an inpatient setting. Additionally, the role of each professional is not clearly defined. Programs for self-management and education that include content, assessments of duration, contact frequency, and delivery techniques should be established.

In conclusion, a multidisciplinary care team comprised of five or more professionals may be linked to a better prognosis for kidney disease and overall mortality. Furthermore, multidisciplinary team-based treatment is expected to be effective for CKD other than diabetes. To manage patients holistically, multidisciplinary care integrates several professionals and is patient-centered. A multidisciplinary care team should be delivered by nephrologists and other professionals, not only CKDEs such as trained nurses, dieticians, and pharmacists but also physical therapists and social workers, ideally with an understanding of CKD.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data used in this article are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: MA, TH, TS
Data curation: All authors
Formal analysis: MA
Funding acquisition: MA, SK
Investigation, Methodology: TH, YI, TS
Writing–original draft: MA
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Inpatient multidisciplinary care can prevent deterioration of renal function in patients with chronic kidney disease: a nationwide cohort study

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Background: Multidisciplinary care is necessary to prevent worsening renal function and all-cause mortality in patients with chronic kidney disease (CKD) but has mostly been investigated in the outpatient setting. In this study, we evaluated the outcome of multidisciplinary care for CKD according to whether it was provided in an outpatient or inpatient setting.

Methods: This nationwide, multicenter, retrospective, observational study included 2954 Japanese patients with CKD stage 3–5 who received multidisciplinary care in 2015–2019. Patients were divided into two groups: an inpatient group and an outpatient group, according to the delivery of multidisciplinary care. The primary composite endpoint was the initiation of renal replacement therapy (RRT) and all-cause mortality, and the secondary endpoints were the annual decline in the estimated glomerular filtration rate (ΔeGFR) and the changes in proteinuria between the two groups.

Results: Multidisciplinary care was provided on an inpatient basis in 59.7% and on an outpatient basis in 40.3%. The mean number of health care professionals involved in multidisciplinary care was 4.5 in the inpatient group and 2.6 in the outpatient group ($P < 0.0001$). After adjustment for confounders, the hazard ratio of the primary composite endpoint was significantly lower in the inpatient group than in the outpatient group (0.71, 95% confidence interval 0.60-0.85, P = 0.0001). In both groups, the mean annual ΔeGFR was significantly improved, and proteinuria significantly decreased 24 months after the initiation of multidisciplinary care.

Conclusion: Multidisciplinary care may significantly slow deterioration of eGFR and reduce proteinuria in patients with CKD and be more effective in terms of reducing initiation of RRT and all-cause mortality when provided on an inpatient basis.

KEYWORDS

certified kidney disease educator, chronic kidney disease, estimated glomerular filtration rate, inpatient educational program, multidisciplinary care, outpatient guidance, renal replacement therapy

1 Introduction

Increasing numbers of patients have chronic kidney disease (CKD) worldwide (1). In Japan, nearly 15 million adults were estimated to have CKD in 2015 (2), and increasing numbers of patients with end-stage kidney disease are starting renal replacement therapy (RRT) each year, with more than 340,000 patients now receiving dialysis (3). The prevalence of dialysis in Japan is 2682 per million population, second only to Taiwan (4). A comprehensive approach to management is needed because CKD increases the risk of not only ESKD but also cardiovascular mortality. Thus it is necessary to control blood pressure, glycemic status, anemia, bone mineral status, and low-density lipoprotein cholesterol alongside lifestyle modification, dietary guidance, and measures to ensure adherence with medication (5, 6). It has been reported that comprehensive multidisciplinary care can reduce all-cause mortality, the likelihood of temporary catheterization for patients on dialysis, and the hospitalization rate as well as slow decline in the estimated glomerular filtration rate (eGFR) (7–10). In these studies, comprehensive multidisciplinary care was provided by teams that included nephrologists, specialist nurses, dieticians, pharmacists, and social workers.

The Certified Kidney Disease Educator (CKDE) system was established in Japan by the Japan Kidney Association in 2017 with the aims of preventing progression of CKD and improving and maintaining quality of life for patients with CKD. Nurses, registered dieticians, and pharmacists who meet certain requirements are eligible to qualify as a CKDE. All CKDEs have acquired the basic skills for managing patients with CKD, including providing guidance on lifestyle modification, dietary counseling, and medical therapy according to disease stage. Generally, multidisciplinary care for patients with CKD and diabetes is performed on an outpatient basis, as reflected in the Steno-2 and MASTERPLAN studies (11–14). However, in Japan, widespread multidisciplinary care for patients with CKD is provided not only on an outpatient basis but also on an inpatient basis because of lack of time during outpatient appointments to cover lifestyle modification, dietary restriction, and medication adherence in sufficient depth. Currently, however, there is limited information on whether these multidisciplinary interventions in the inpatient setting improve the prognosis of CKD.

We conducted this nationwide study to assess the outcome of multidisciplinary intervention in patients with CKD according to whether it was provided in an outpatient or inpatient setting.

2 Methods

2.1 Study design and participants

This nationwide multicenter retrospective cohort study was performed by members of the Japan Kidney Association Committee for Evaluation and Dissemination of CKDE. To reflect practice patterns across most of Japan, around 3000 Japanese patients were participated at any of 24 selected health care institutions in Japan that play a central role in the treatment of patients with CKD. All-cause mortality and the start of RRT were tracked until the end of 2020 for patients with CKD who had data on kidney function available for the 12 months before to and 24 months after receiving multidisciplinary therapy between January 2015 and December 2019. The following exclusion requirement were used: age < 20 years; CKD stage 1 and 2 (i.e., eGFR ≥ 60 mL/min/1.73 m^2); patients who were hospitalized for another reason other than CKD; short-term follow-up of 6 months or less; received multidisciplinary care in the past; active malignant disease; transplant recipient; history of long-term dialysis; and data missing for age, sex, kidney function, or results. In Japan, multidisciplinary care for patients with CKD was conducted in outpatient or inpatient settings based on the hospital functions, nephrologists' judgment, and the patient's wishes. As a result, the enrolled patients were classified into an outpatient and an inpatient group based on the approach and place of intervention by the multidisciplinary care team at the start of the intervention (baseline). They were further divided into subgroups based on whether they had diabetes. A group of inpatient patients were admitted to the hospital and received multidisciplinary care in accordance with each facility's inpatient educational program.

The main efficacy composite endpoint was the initiation of RRT and all-cause mortality at the end of 2020. The secondary efficacy endpoint was the annual decline in eGFR (ΔeGFR) and the annual change in urinary protein level between 12 months before and 6, 12, and 24 months after the initiation of multidisciplinary intervention.

The study was approved by the ethics committee of Nihon University Itabashi Hospital and conducted in accordance with the Declaration of Helsinki, Japanese privacy protection laws, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare in 2015. The need for informed consent was waived in view of the use of de-identified data. The study is registered in the University Hospital Medical Information Network (UMIN000049995).

2.2 Multidisciplinary care

The definition of multidisciplinary care adopted was (1) a multidisciplinary care team composed of nephrologists and other professionals (i.e., specialist nurses, registered dieticians, pharmacists, physical therapists, social workers, clinical engineers, and clinical laboratory technicians) and (2) an operational model of multidisciplinary care comprising patient education, medical management, and lifestyle modification according to CKD stage. The quality of the educational content provided was maintained based on the text created by the Japanese Society of Nephrology, the Japanese Society for Dialysis Therapy, the Japan Society for Transplant, and the Japanese Society for Clinical Renal Transplantation or the CKD Teaching Guidebook for Certified Kidney Disease Educators published by the Japan Kidney Association (15, 16).

2.3 Data collection

Patient demographics and data on clinical characteristics were collected, including age, sex, history of cardiovascular disease (CVD), primary etiology of CKD, body mass index (BMI), hemoglobin, serum albumin, urea nitrogen, creatinine (Cr), eGFR, and urinary protein. Information on glycated hemoglobin (HbA1c) was also collected for patients with diabetes at baseline. CVD was defined as coronary artery disease, ischemic stroke, hemorrhagic stroke, or limb amputation. eGFR was calculated according to the following formula for Japanese patients: eGFR (mL/min/1.73 m^2) = 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ (× 0.739 for women) (17). Urinary protein was calculated as the urinary protein to Cr ratio (UPCR). The data on method and place of intervention (outpatient or inpatient), the number or duration of interventions (number of visits for outpatient intervention or the number of hospitalization days for inpatients), and the type and number of health care professionals involved in the multidisciplinary care team were also collected. Data were collected for the primary composite endpoint, which included the date attained or the end of 2020, whichever came first (initiation of RRT and all-cause mortality). Also noted was the RRT's kind (kidney transplantation, peritoneal dialysis, or hemodialysis).

2.4 Statistical analysis

Data are reported as the number and proportion, mean ± standard deviation, or median [interquartile range] as appropriate. Intragroup comparisons were made using two-tailed paired t-tests. Categorical variables were examined using the chi-squared test and continuous variables using the t-test. The composite outcome was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. A univariate analysis was performed according to the method and place of intervention (i.e., outpatient-based or inpatient-based). Multivariate survival analyses were performed using Cox proportional hazards models with adjustment for confounding factors to examine the method and place of intervention and the composite outcome during the 6 years of follow-up. Model 1 was used to calculate hazard ratios (HRs) adjusted for basic factors, including age, sex, history of CVD, eGFR, and UPCR at baseline, and model 2 was adjusted for BMI, hemoglobin, and serum albumin level in addition to the factors included in model 1. A subgroup analysis was performed according to the diabetes status and the CKD stage (G3a, G3b, G4, or G5) at baseline. A further subdivision analysis in the inpatient group based on the presence or absence of physical therapists was performed. In patients with diabetes, model 1 was used to calculate the HRs with adjustment for basic factors (e.g., age, sex, history of CVD, HbA1c, eGFR, and UPCR at baseline), and model 2 was adjusted for BMI, hemoglobin, and serum albumin level in addition to the factors included in model 1. In patients without diabetes, model 1 was used to calculate the HRs adjusted for basic factors, including age, sex, history of CVD, eGFR, and UPCR at baseline and model 2 was adjusted for BMI, hemoglobin, and serum albumin level in addition to the factors included in model 1. The results from the models are reported as HRs with 95% confidence intervals (CIs) and P-values. For the regression analyses, imputation of missing data was performed by conventional methods as appropriate. All analyses were performed using JMP® version 13.0 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at P-values less than 0.05.

3 Results

3.1 Patient characteristics at time of initiation of multidisciplinary care

Overall, of the 3296 patients enrolled, 342 were removed (CKD stage 1 or 2, n = 118; age younger than 20 years, n = 3; follow-up for 6 months or less, n = 124; lack of data for baseline kidney function, n = 13), which left 2954 patients for inclusion in the analysis. Patient characteristics at the time of initiation of multidisciplinary care are shown in Table 1. The mean age was 70.5 ± 11.6 years, and 74.1% of the patients were male. The mean eGFR was 26.3 ± 12.5 mL/min/1.73 m^2 and the median UPCR was 1.09 g/gCr [0.23, 2.98]. The most common etiology of CKD was diabetic kidney disease (42.7%), followed by nephrosclerosis (30.8%) and chronic

TABLE 1 Baseline characteristics of all study participants.

Variable	
Patients, n (% male)	2954 (74.1)
Age, years	70.5 ± 11.6
Body mass index	24.2 ± 4.3
Serum creatinine, mg/dL	2.02 [1.46, 3.02]
eGFR, mL/min/1.73 m^2	26.3 ± 12.5
Serum urea nitrogen, mg/dL	31 [23–43]
Hemoglobin, g/dL	11.7 ± 1.9
Serum albumin, g/dL	3.8 ± 0.5
Urinary protein, g/gCr	1.09 [0.23, 2.98]
Comorbid CVD, n (%)	846 (28.6)
HbA1c (in patients with diabetes), %	6.4 ± 1.0
Primary cause of CKD, n (%)	
Diabetic kidney disease	1263 (42.7)
Nephrosclerosis	909 (30.8)
Chronic glomerulonephritis	374 (12.6)
Polycystic kidney disease	87 (3.0)
Other	321 (10.9)
CKD stage, n (%)	
G3 (G3a + G3b)	1059 (35.9)
G3a	288 (9.8)
G3b	771 (26.1)
G4	1251 (42.4)
G5	644 (21.8)
Number of professionals on MDC team, n (%)	
Total number of professionals on MDC team, n	3.8 ± 1.2
2	656 (22.2)
3	398 (13.5)
4	902 (30.5)
5	976 (33.0)
6	22 (0.8)
Members of MDC team, n (%)	
Nurses	2545 (86.2)
Registered dieticians	2703 (91.5)
Pharmacists	1885 (63.8)
Physical therapists	772 (26.1)
Clinical laboratory technicians	171 (5.8)
Social workers	68 (2.3)
Others	24 (0.8)

Data are shown as the number (percentage), mean ± standard deviation, or median [interquartile range] as appropriate. CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MDC, multidisciplinary care.

glomerulonephritis (12.6%). The most common CKD stage was G4 (42.4%), followed by G3b (26.1%) and G5 (21.8%).

3.2 Type and number of professionals in the multidisciplinary care team

Details of the interventions implemented by the multidisciplinary care team are shown in Table 1. The mean number of multidisciplinary care team members, including nephrologists, was 3.8 ± 1.2. It was most common for the multidisciplinary care team to include five professionals (33.0%), followed by four (30.5%) and the two (22.2%). Registered dieticians were the most common members of the multidisciplinary care team (91.5%), followed by specialist nurses (86.2%), pharmacists (63.8%), and physical therapists (26.1%).

3.3 Outcomes

The median observation period was 36 months [22, 52], during which 128 patients (4.3%) died, 648 (21.9%) initiated RRT, and 66 (2.2%) were lost to follow-up; 2112 (71.6%) of all patients were alive without RRT at the end of the study period. RRT consisted of hemodialysis in 559 patients (86.2%), peritoneal dialysis in 66 (10.2%), and kidney transplantation in 23 (3.6%).

3.3.1 Comparison between outpatient and inpatient groups

The baseline characteristics of the patients in the inpatient and outpatient groups are shown in Table 2. Intervention was provided in an inpatient setting for more than half of the patients (59.7%) and on an outpatient basis for the remainder (40.3%). The baseline kidney function, including eGFR, serum Cr and UPCR, was comparable between the two groups, but patients in the inpatient group were more likely to be female and older and to have a higher BMI and comorbid CVD. However, rates of diabetic kidney disease and CKD stage G5 were lower in the inpatient group than in the outpatient group. The mean number of multidisciplinary care team members was significantly higher in the inpatient group (4.5 ± 0.6 *vs*. 2.6 ± 0.7, P < 0.0001).

Kaplan–Meier analysis for the composite endpoint (initiation of RRT and all-cause mortality) revealed a significant difference between the outpatient and inpatient groups (P = 0.0003, log-rank test; Figure 1). Compared with the outpatient (reference) group, the inpatient group had a significantly lower unadjusted HR for the composite endpoint (0.78, 95% CI 0.68–0.91, P = 0.0004). After adjustment for basic factors, including age, sex, history of CVD, eGFR, and UPCR at baseline, the HR in the inpatient group was 0.73 (95% CI 0.63–0.88, P = 0.0001). After further adjustment for basic factors and BMI, hemoglobin, and serum albumin at baseline, the HR was significantly lower in the inpatient group (0.71, 95% CI 0.60–0.85, P = 0.0001) (Table 3).

3.4 Subgroup analysis according to diabetes status

Kaplan–Meier analysis revealed that there was no significant difference in the composite endpoint between patients with diabetes in the outpatient group and those in the inpatient group (P = 0.133, log-rank test; Figure 2). Cox proportional analysis revealed no significant difference in the unadjusted HR for the composite endpoint between the inpatient and outpatient groups (Table 4). However, after adjustment for basic factors, including age, sex, history of CVD, HbA1c, eGFR, and UPCR at baseline, the HR in the inpatient group was 0.75 (95% CI 0.61–0.93, P = 0.010). After further adjustment for basic factors and BMI, hemoglobin, and serum albumin level at baseline, the inpatient group had a significantly lower HR (0.74, 95% CI 0.59–0.95, P = 0.018) (Table 4).

In patients without diabetes, Kaplan–Meier analysis revealed a significant difference in the composite endpoint between the outpatient and inpatient groups (P = 0.009, log-rank test; Figure 3). Compared with the outpatient group, the inpatient group had a significantly lower unadjusted HR for the composite endpoint (0.75, 95% CI 0.61–0.93, P = 0.009). After adjustment for basic factors, including age, sex, history of CVD, eGFR, and UPCR at baseline, the HR in the inpatient group was 0.75 (95% CI 0.59–0.94, P = 0.015). After further adjustment for basic factors and BMI, hemoglobin, and serum albumin level at baseline, the inpatient group had a significantly lower HR (0.76, 95% CI 0.59–0.98, P = 0.034) (Table 5).

3.5 Subgroup analysis according to the CKD stage at baseline

All-cause mortality and RRT initiation were dependent on the disease stage. The Kaplan–Meier analysis revealed that the composite endpoint varied significantly depending on the CKD stage at baseline in both groups (P < 0.0001, log-rank test; Figure 4). After the adjustment of basic factors, including age, sex, comorbid CVD, and the presence or absence of diabetes, the HRs in the G3b, G4, and G5 groups were compared with the G3a (reference) group and were significantly higher in both. However, after the adjustment of basic factors and laboratory data, including BMI, hemoglobin, serum albumin, and UPCR level, the G4 and G5 groups had significantly higher HRs (Tables 6, 7).

3.6 Subgroup analysis based on the presence or absence of physical therapists in the inpatient group

The patients in the inpatient group were subdivided into two groups with and without a physical therapist in the

TABLE 2 Baseline characteristics in the outpatient and inpatient groups.

Variable	Outpatient group	Inpatient group	P-value
Patients, n (% male)	1190 (79.3)	1764 (70.6)	< 0.0001
Age, years	69.6	71.2	0.0004
Body mass index	23.6 ± 3.9	24.5 ± 4.4	< 0.0001
Serum creatinine, mg/dL	2.08 [1.45, 3.16]	1.99 [1.47, 2.93]	0.165
eGFR, mL/min/1.73 m^2	26.1 ± 12.9	26.4 ± 12.3	0.786
Serum urea nitrogen, mg/dL	32 [23, 45]	31 [23, 42]	0.239
Hemoglobin, g/dL	11.8 ± 1.9	11.7 ± 1.9	0.123
Serum albumin, g/dL	3.8 ± 0.5	3.7 ± 0.5	< 0.0001
Urinary protein, g/gCr	1.20 [0.27, 3.25]	1.01 [0.22, 2.87]	0.218
Comorbid CVD, n (%)	334 (28.1)	512 (29.0)	< 0.0001
HbA1c (in patients with diabetes), %	6.4 ± 0.9	6.4 ± 1.1	0.188
Primary cause of CKD, n (%)			< 0.0001
Diabetic kidney disease	579 (48.6)	684 (38.8)	
Nephrosclerosis	259 (21.8)	650 (36.8)	
Chronic glomerulonephritis	126 (10.6)	248 (14.0)	
Polycystic kidney disease	45 (3.8)	42 (2.4)	
Others	321 (15.2)	140 (8.0)	
CKD stage, n (%)			0.005
G3 (G3a + G3b)	431 (36.2)	624 (35.6)	
G3a	129 (10.8)	159 (9.0)	
G3b	302 (25.4)	469 (26.6)	
G4	469 (39.4)	782 (44.3)	
G5	290 (24.4)	354 (20.1)	
Number of interventions, n or days	4 [1, 10]	7 [5, 12]	—
Total number of professionals on MDC team, n	2.6 ± 0.7	4.5 ± 0.6	< 0.0001
Number of professionals on MDC team, n (%)			< 0.0001
2	641 (53.9)	17 (1.0)	
3	363 (30.5)	33 (1.9)	
4	178 (15.0)	724 (41.0)	
5	6 (0.5)	970 (55.0)	
6	2 (0.1)	20 (1.1)	
Members of MDC team, n (%)			
Nurses	790 (66.4)	1755 (99.5)	< 0.0001
Registered dieticians	948 (79.6)	1755 (99.5)	< 0.0001
Pharmacists	172 (14.5)	1713 (97.1)	< 0.0001
Physical therapists	0 (0)	772 (43.8)	< 0.0001
Clinical laboratory technicians	0 (0)	171 (9.7)	< 0.0001

(Continued)

TABLE 2 Continued

Variable	Outpatient group	Inpatient group	P-value
Social workers	5 (0.4)	63 (3.6)	< 0.0001
Others	21 (1.8)	3 (0.2)	< 0.0001

Data are shown as the number (percentage), mean ± standard deviation, or median [interquartile range] as appropriate. CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MDC, multidisciplinary care.

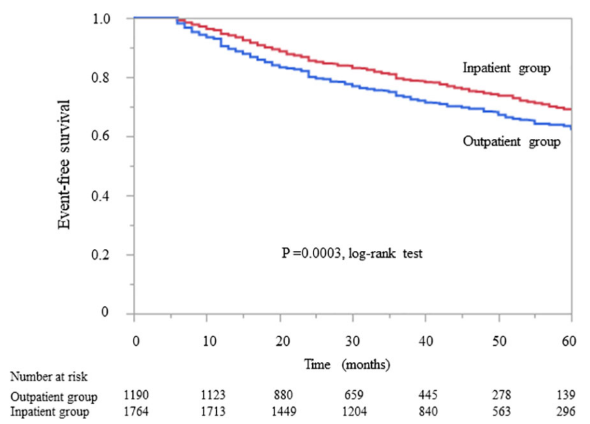

FIGURE 1
Kaplan–Meier curves showing the incidence of initiation of renal replacement therapy and all-cause mortality in Japanese patients with chronic kidney disease according to whether they received outpatient or inpatient multidisciplinary care.

multidisciplinary care team. The baseline characteristics of the two groups are shown in Supplementary Table 1. The group with physical therapists had higher eGFR and lower proteinuria at baseline, with a higher rate of comorbid CVD and diabetic kidney disease. The Kaplan–Meier analysis revealed a significant difference in the composite endpoint between the two groups (P < 0.0001, log-rank test; Figure 5). Compared with the group without physical therapists, the group with physical therapists had a significantly lower unadjusted HR for the composite endpoint (0.52, 95% CI 0.42–0.63, P < 0.0001). After the adjustment of basic factors, including age, sex, history of CVD, eGFR, and UPCR at baseline, the HR in the group with physical therapists was 0.51 (95% CI 0.41–0.64, P < 0.0001). After further adjustment of basic factors and BMI, hemoglobin, and serum albumin level at baseline, the group with physical therapists had a significantly lower HR (0.55, 95% CI 0.42–0.71, P < 0.0001) (Supplementary Table 2).

3.7 ΔeGFR and change in UPCR before and after multidisciplinary care in all patients

The mean ΔeGFR was significantly improved from −5.89 ± 7.17 before multidisciplinary intervention to −0.44 ± 5.21 at 6 months, −1.52 ± 6.09 at 12 months, and −1.48 ± 3.78 at 24 months after intervention (all P < 0.0001; Figure 6A). The median UPCR was significantly decreased from 1.09 g/gCr [0.23, 2.98] at baseline to 1.00 g/gCr [0.24, 2.71] at 6 months, 0.89 g/gCr [0.21, 2.38] at 12 months, and 0.82 g/gCr [0.20, 2.22] at 24 months (all P < 0.0001; Figure 6B).

3.7.1 ΔeGFR and change in UPCR before and after multidisciplinary care in the two groups

The mean ΔeGFR before and after multidisciplinary intervention in each group is shown in Figure 7. There was no significant between-group difference in mean ΔeGFR before intervention (Supplementary Table 3). The mean ΔeGFR was -6.09 ± 7.65 before intervention and -0.52 ± 5.23 at 6 months, -1.32 ± 6.01 at 12 months, and -1.32 ± 3.64 at 24 months after intervention in the outpatient group (all P < 0.0001; Figure 7A); the respective values in the inpatient group were -5.81 ± 7.43, -0.40 ± 5.20, -1.63 ± 6.15, and -1.56 ± 3.84 (all P < 0.0001; Figure 7B). There was no significant between-group difference in mean ΔeGFR at any time point after intervention (Supplementary Table 3).

Changes in the median UPCR after intervention by the multidisciplinary care team are shown for each group in Figure 8. There was no significant between-group difference in UPCR at baseline. However, in the outpatient group, the median UPCR decreased significantly from 1.20 g/gCr [0.27, 3.25] at baseline to 1.10 g/gCr [0.29, 2.98] at 6 months, 0.94 g/gCr [0.22, 2.42] at 12 months, and 0.88 g/gCr [0.24, 2.36] at 24 months (all P <0.0001; Figure 8A); the respective values in the inpatient group were 1.01 g/gCr [0.22, 2.87], 0.92 g/gCr [0.21, 2.61], 0.82 g/gCr [0.21, 2.37], and 0.79 g/gCr [0.17, 2.28] (all P < 0.0001; Figure 8B). Furthermore, there was no significant between-group difference in the median UPCR at any time point after intervention (Supplementary Table 4).

TABLE 3 Comparison of initiation of renal replacement therapy and all-cause mortality between the outpatient and inpatient groups in Cox proportional hazards models adjusted for confounding factors in Japanese patients with chronic kidney disease.

Group	Unadjusted			Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Outpatient	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Inpatient	0.78	0.68–0.91	0.0004	0.73	0.63–0.88	0.0001	0.71	0.60–0.85	0.0001

Model 1 was adjusted for basic factors, including age, sex, history of cardiovascular disease, estimated glomerular filtration rate, and urinary protein level at baseline. Model 2 was adjusted for body mass index, hemoglobin, and serum albumin level at baseline in addition to the factors included in model 1. CI, confidence interval; HR, hazard ratio.

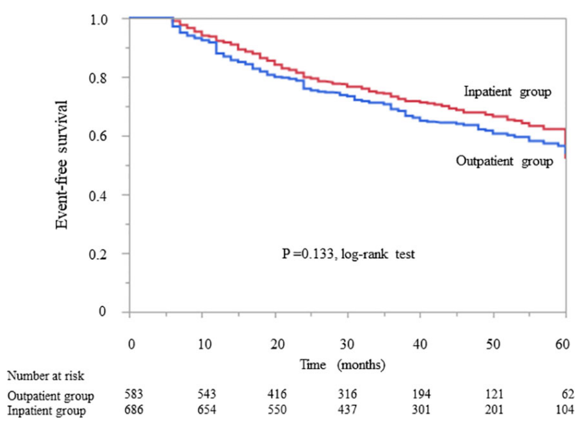

FIGURE 2
Kaplan–Meier curves showing the incidence of initiation of renal replacement therapy and all-cause mortality in Japanese diabetes patients with chronic kidney disease according to whether they received outpatient or inpatient multidisciplinary care.

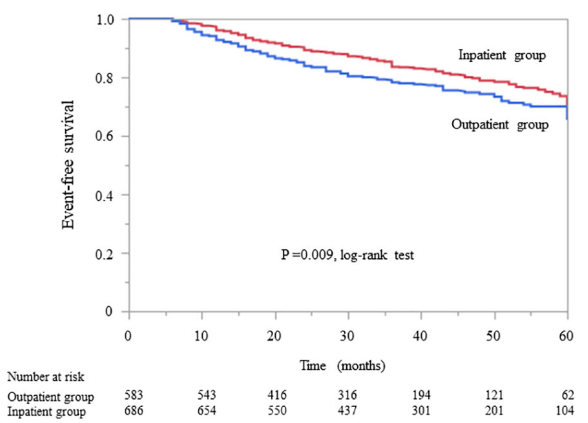

FIGURE 3
Kaplan–Meier curves for the incidence of initiation of renal replacement therapy and all-cause mortality in Japanese non-diabetes patients with chronic kidney disease in the outpatient and inpatient groups.

4 Discussion

This nationwide cohort study included 2954 individuals from 24 facilities in Japan. We found that patients with CKD currently receive multidisciplinary care more often in hospitals (59.7%) than in an outpatient setting (40.3%) in Japan. The major strengths of this study are its large sample population recruited from multiple centers, the relatively long observation period, and inclusion of a comparatively high number of elderly patients. Although the mean age of patients in the previous studies was younger than 70 years, our mean age was 70.5 years, reflecting our aging CKD population in Japan (5, 7–10). This study is the first to suggest that multidisciplinary care may be able to prevent worsening kidney function in Japanese patients with CKD regardless of whether it is provided on an outpatient or inpatient basis. The rate of RRT initiation and all-cause mortality over the longer observation period of 6 years were the key composite endpoints, and although there was no significant difference between the two groups' baseline eGFR levels, there was a significant between-group difference in both variables. Therefore, our results suggest that multidisciplinary care for patients with CKD might be more beneficial in terms of outcomes in the inpatient setting than in the outpatient setting. Furthermore, multidisciplinary care was effective for patients with CKD regardless of whether or not they had diabetes and should be provided at CKD stage G4 at the latest. A multidisciplinary care team should include a nephrologist, a specialist nurse, a physical therapist, and professionals from other fields and is recommended for the management of patients with CKD.

Inpatient education programs have been reported to improve glycemic control, prevent diabetic complications, and reduce hospitalization rates in patients with diabetes (18–20). However, there is little information on the efficacy of multidisciplinary intervention for patients with CKD according to whether the intervention is inpatient-based or outpatient-based. This is the first study to indicate that inpatient multidisciplinary care improves the all-cause mortality risk and initiation of RRT in patients with CKD. Inpatient education programs for patients with CKD have not been implemented extensively in Western countries, probably reflecting differences in the medical insurance system between Japan and Western countries. Although education provided in an outpatient setting is reimbursed for patients with diabetic kidney disease in Japan, it is not reimbursed for patients with other etiologies of CKD. However, full reimbursement is available for these patients if they are admitted to hospital. A few single-center studies in Japan have evaluated the effectiveness of education programs for CKD to date. One study found that the annual rate of decline in eGFR was improved by an inpatient education program, which was continued for 2 years (21). Furthermore, the interval between the start of stage G5 and the start of RRT was longer in patients who received an inpatient education program than in those who did not (22). The patients who received an inpatient education program also had better survival after initiation of dialysis (23). Therefore, multidisciplinary care would be associated with a decreased hospitalization rate, a

TABLE 4 Comparison of initiation of renal replacement therapy and all-cause mortality between the outpatient and inpatient groups in Cox proportional hazards models adjusted for confounding factors in Japanese patients with chronic kidney disease and diabetes.

Group	Unadjusted			Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Outpatient	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Inpatient	0.86	0.71–1.05	0.138	0.75	0.61–0.93	0.01	0.74	0.59–0.95	0.018

Model 1 was adjusted for basic factors, including age, sex, history of cardiovascular disease, glycated hemoglobin, estimated glomerular filtration rate, and urinary protein level at baseline. Model 2 was adjusted for body mass index, hemoglobin, and serum albumin at baseline in addition to the factors included in model 1. CI, confidence interval; HR, hazard ratio.

TABLE 5 Comparison of all-cause mortality between the outpatient and inpatient groups according to Cox proportional hazards models adjusted for confounding factors in Japanese patients with chronic kidney disease but no diabetes.

Group	Unadjusted			Model 1			Model 2		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Outpatient	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Inpatient	0.75	0.61–0.93	0.009	0.75	0.59–0.94	0.015	0.76	0.59–0.98	0.034

Model 1 was adjusted for basic factors, including age, sex, history of cardiovascular disease, estimated glomerular filtration rate, and urinary protein level at baseline. Model 2 was adjusted for body mass index, hemoglobin, and serum albumin at baseline in addition to the factors included in model 1. CI, confidence interval; HR, hazard ratio.

longer time until initiation of dialysis, and a shorter hospital stay at the start of dialysis, which could lead to a reduction of medical costs. However, the content of the education program and the delivered systems varied according to each facility. Nevertheless, the number of days of hospitalization and the time spent on education should be analyzed. Also, the reasons why it could not be achieved on an outpatient basis should be confirmed. Therefore, further research is required to confirm that the cost-effectiveness of the inpatient setting is superior to that of the outpatient setting.

A meta-analysis revealed that the reduction in all-cause mortality depended on the disciplines represented in the multidisciplinary care team and the stage (24). With only nephrologists and specialist nurses on the team, there was no significant difference in all-cause mortality between patients receiving multidisciplinary care and those who were not. By contrast, when the multidisciplinary care team comprised nephrologists, specialist nurses, and professionals from other disciplines (e.g., dieticians, pharmacists, or social workers), multidisciplinary care was associated with a lower risk of all-cause mortality (25). The FROM-J (Frontier of Renal Outcome Modifications in Japan) study reported that lifestyle and dietary advice provided by a registered dietician in an outpatient setting slowed the rate of deterioration of kidney function in patients with CKD when compared with controls (26). However, the findings were not significant for all stages of CKD and were limited to stage 3; moreover, the multidisciplinary care team comprised only doctors and registered dieticians. In our study, multidisciplinary care was provided by a mean of 4.5 ± 0.6 professionals in the inpatient group and by 2.6 ± 0.7 in the outpatient group. A possible explanation for this result is that when the multidisciplinary care team consists of nephrologists and nurses, the multidisciplinary care model is similar to a conventional model, in which non-multidisciplinary care may be provided by nephrologists and nurses. When the multidisciplinary care group does not include other professionals (e.g., registered dieticians and pharmacists), the education provided for patients with CKD may be insufficient, such that guidelines for dietary protein restriction and other targets are not met, thereby contributing to worsening of kidney function. Patients with CKD require holistic care and support, including dietary modification, maintenance and improvement of medication adherence, education on self-monitoring and early detection of complications, and adequate financial resources to continue treatment. These supports cannot be provided by nephrologists alone and must be implemented by a medical team consisting of multiple professionals. To achieve good outcomes, multidisciplinary care teams that include nephrologists, nurses, registered dieticians, pharmacists, physical therapists, and medical social workers should be involved and have shared goals in terms of individual patients. However, we have no definitive conclusions on how many different cooperating disciplines are needed to achieve optimal outcomes, and further investigations are required to confirm this.

This study has several limitations. First, it did not include a non-multidisciplinary control group. Although multidisciplinary care was not associated with a lower risk of all-cause mortality in previous randomized controlled trials, the risk was found to be reduced in one cohort study (14, 26–28). In addition, the patients could not be randomly allocated to outpatient and inpatient groups because the environment in which multidisciplinary care could be provided varied depending on each facility. Therefore, further prospective randomized

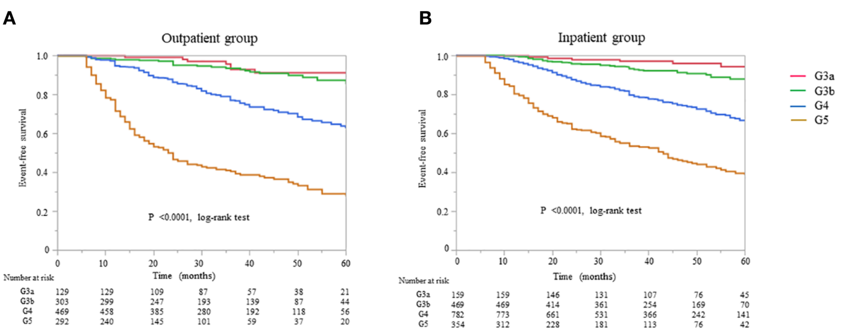

FIGURE 4
Kaplan–Meier curves for the incidence of initiation of renal replacement therapy and all-cause mortality in Japanese patients with chronic kidney disease according to the baseline stages in the (A) outpatient and (B) inpatient groups.

TABLE 6 All-cause mortality and initiation of renal replacement therapy according to the CKD stage at baseline in Cox proportional hazards models adjusted for confounding factors in the outpatient group.

Group	Unadjusted			Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
G3a	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
G3b	2.63	1.21–6.92	0.013	1.76	0.80–4.42	0.164	1.41	0.57–3.99	0.468
G4	7.87	3.82–20.0	<0.0001	5.65	2.83–13.4	<0.0001	3.65	1.67–9.59	0.001
G5	22.8	11.1–58.9	<0.0001	21.0	10.63–49.7	<0.0001	12.8	5.91–33.8	<0.0001

Model 1 was adjusted for basic factors, including age, sex, history of cardiovascular diseases, presence or absence of diabetes, and urinary protein levels at baseline. Model 2 was adjusted the same as Model 1 but with additional adjustments for body mass index, hemoglobin, and serum albumin levels at baseline. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

TABLE 7 All-cause mortality and initiation of renal replacement therapy according to the CKD stage at baseline in Cox proportional hazards models adjusted for confounding factors in the inpatient group.

Group	Unadjusted			Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
G3a	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
G3b	2.63	1.21–6.92	0.013	2.94	1.34–7.73	0.005	2.18	0.98–5.80	0.056
G4	7.87	3.82–20.0	<0.0001	9.08	4.38–23.1	<0.0001	5.58	2.64–14.3	< 0.0001
G5	22.8	11.1–58.9	<0.0001	27.9	13.5–71.5	<0.0001	15.2	7.10–39.8	< 0.0001

Model 1 was adjusted for basic factors, including age, sex, history of cardiovascular diseases, presence or absence of diabetes, and urinary protein levels at baseline. Model 2 was adjusted the same as Model 1 but with additional adjustments for body mass index, hemoglobin, and serum albumin levels at baseline. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

controlled trials and large epidemiological studies that include control groups are needed to confirm the efficacy of multidisciplinary care in patients with CKD. Second, we did not investigate changes in blood pressure or laboratory findings other than for kidney function. Salt restriction by multidisciplinary intervention may have lowered blood pressure, reduced proteinuria, and maintained kidney function. We were unable to investigate whether there was any difference in the reduction of salt intake or blood pressure between the study groups.

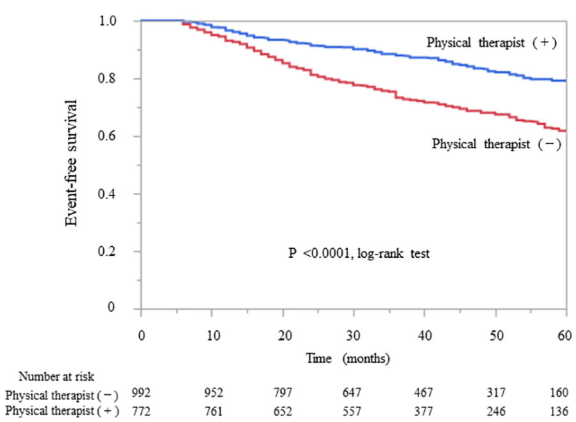

FIGURE 5
Kaplan–Meier curves for the initiation of renal replacement therapy and all-cause mortality in Japanese patients with chronic kidney disease based on the presence or absence of physical therapists in the inpatient subgroups.

Third, adding or changing medications during the observation period might have affected laboratory findings and kidney function. Renin–angiotensin system inhibitors and sodium-glucose cotransporter-2 inhibitors are recommended for patients with albuminuria, and statins are recommended for all patients with diabetes and CKD (29). Treatment of renal anemia with erythropoiesis-stimulating agents plays an important role in kidney survival (30, 31). Further investigations are needed to determine the contribution of improved adherence with prescribed medication and dietary modification to prevention of worsening kidney function. Finally, there may have been some degree of patient selection and facility bias. Inpatient programs are longer and more expensive than outpatient programs. It is possible that the inpatient group included patients with high self-management ability and a strong desire to prevent progression of their CKD. Therefore, multidisciplinary care in an inpatient setting may be associated with improved patient health literacy. In this study, the participants were divided into two groups by the first intervention method. Therefore, some patients may have been treated in both the inpatient and outpatient settings. Patients might have received multidisciplinary care as an inpatient first, followed by an outpatient setting, or vice versa. However, most facilities in this study provided outpatient or inpatient educational programs based on the hospital functions and human resources. In addition, the content of the education program and the makeup of the patient population varied between the outpatient and inpatient groups from facility to facility. Therefore, the effects of simultaneous participation in outpatient and inpatient sessions should be verified, and educational programs should be standardized to improve the level of care for patients with CKD.

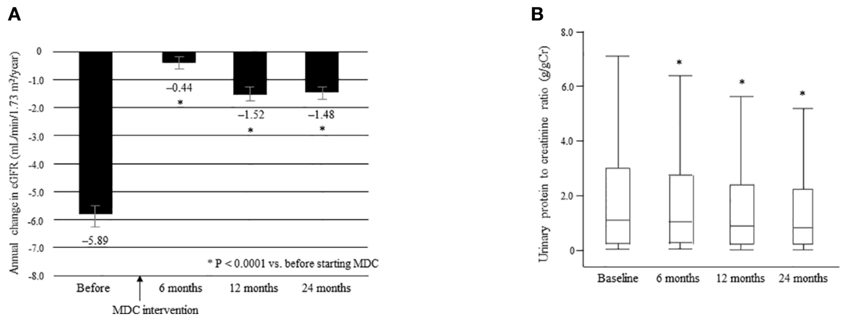

FIGURE 6
Annual change in eGFR in the 12 months before and 24 months after starting multidisciplinary care in all patients **(A)**. Data are shown as the mean. Bars indicate the 95% confidence interval. *P < 0.0001 *vs*. before start of MDC. Changes in the urinary protein level between time of initiation of MDC and 24 months later **(B)**. Data are shown as the median and interquartile range. *P < 0.0001 *vs*. baseline. ΔeGFR, change in eGFR; eGFR, estimated glomerular filtration rate; MDC, multidisciplinary care.

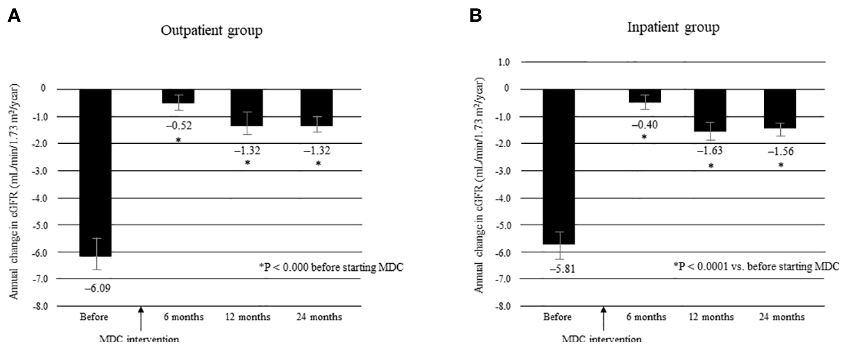

FIGURE 7
Annual change in eGFR in the 12 months before and 24 months after starting MDC in the outpatient group **(A)** and in the inpatient group **(B)**. *P < 0.0001 *vs*. before start of MDC. Data are shown as the mean. Bars indicate the 95% confidence interval. ΔeGFR, change in eGFR; eGFR, estimated glomerular filtration rate; MDC, multidisciplinary care.

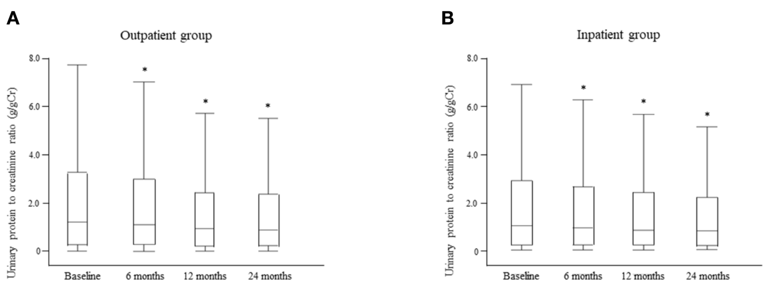

FIGURE 8
Changes in the urinary protein level between the time of starting multidisciplinary care and 24 months later in the outpatient **(A)** and inpatient **(B)** groups. Data are shown as the median and interquartile range. *P < 0.0001 *vs*. baseline.

In conclusion, our findings indicate that multidisciplinary care may significantly slow the decline of eGFR, reduce proteinuria in patients with CKD and be effective regardless of diabetes status. Furthermore, this study suggests that multidisciplinary care might be more effective when inpatient-based than when outpatient-based in terms of reducing the all-cause mortality risk and initiation of RRT. Further research is needed to devise a standardized program of multidisciplinary care for both outpatients and inpatients with CKD and to determine which professionals should be involved to achieve the best outcomes for these patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The ethics committee of Nihon University Itabashi Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MA wrote the manuscript and analyzed the data. TH, YI, TS, and SK designed the study and contributed to data collection. MA, TH, YI, TS, and SK discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript. All authors contributed to the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1180477/full#supplementary-material

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令和 6 年 4 月 1 日

厚生労働大臣　殿

機関名 杏林大学

所属研究機関長　職　名　学長

氏　名　渡邊 卓

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　腎疾患対策研究事業

2．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

3．研究者名　（所属部署・職名）　医学部　腎臓・リウマチ膠原病内科学　客員教授

（氏名・フリガナ）　要 伸也（カナメ シンヤ）

4．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	■	□	■	杏林大学	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

6．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

令和６年４月１日

厚生労働大臣　殿

機関名　学校法人川崎学園川崎医科大学

所属研究機関長　職　名　学長

氏　名　砂田　芳秀

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患政策研究事業

２．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

３．研究者名　（所属部署・職名）　医学部・学長付特任教授

（氏名・フリガナ）　柏原　直樹・カシハラ　ナオキ

４．倫理審査の状況

	該当性の有無 有	該当性の有無 無	左記で該当がある場合のみ記入 (※1) 審査済み	審査した機関	未審査 (※2)
人を対象とする生命科学・医学系研究に関する倫理指針 (※3)	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

厚生労働大臣　殿

令和 6 年 4 月 24 日

機関名　埼玉医科大学

所属研究機関長　職　名　学長

氏　名　竹内　勤

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患対策研究事業

２．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

３．研究者名　（所属部局・職名）　医学部・教授

（氏名・フリガナ）　岡田　浩一・オカダ　ヒロカズ

４．倫理審査の状況

	該当性の有無 有	該当性の有無 無	左記で該当がある場合のみ記入 (※1) 審査済み	審査した機関	未審査 (※2)
人を対象とする生命科学・医学系研究に関する倫理指針 (※3)	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

厚生労働大臣　殿

令和　6年　4月　26日

機関名　日本大学医学部

所属研究機関長　職　名　医学部長

氏　名　木下浩作

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　腎疾患対策研究事業

2．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

3．研究者名　（所属部署・職名）　内科学系腎臓高血圧内分泌内科学分野・教授

（氏名・フリガナ）　阿部　雅紀（アベ　マサノリ）

4．倫理審査の状況

	該当性の有無 有	該当性の有無 無	左記で該当がある場合のみ記入（※1） 審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	■	□	■	日本大学医学部附属板橋病院	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

6．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 ■　無 □（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。

令和６年１月１５日

厚生労働大臣　殿

機関名　国立大学法人大阪大学

所属研究機関長　職　名　大学院医学系研究科長

氏　名　熊ノ郷　淳

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患政策研究事業

２．研究課題名　慢性腎臓病（CKD）患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

３．研究者名　（所属部署・職名）　大学院医学系研究科・教授

（氏名・フリガナ）　猪阪　善隆・イサカ　ヨシタカ

４．倫理審査の状況

	該当性の有無 有	無	左記で該当がある場合のみ記入（※1） 審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	■	□	■	大阪大学医学部附属病院	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

大阪大学医学系研究科では、厚生労働科学研究費補助金に係る承諾書等について以下のとおり取扱っております。

Ⅰ．厚生労働科学研究費補助金の研究実施承諾書・倫理審査状況及び利益相反等報告書について

本学では、厚生労働科学研究費補助事業の研究実施の承諾については、従来より研究者が所属する各部局長より行なっております。

これは「大阪大学教授会通則」第4条に基づき、各部局の教授会が各部局の教育・研究に関する重要事項の決定権を有しているため、教授会の責任者である部局長が研究実施に対する承諾権限を有しているとみなしているためです。

そのため、大阪大学医学系研究科に所属している研究者の研究実施の承諾は医学系研究科長より行っております。

同様に、倫理審査状況及び利益相反等報告書についても医学系研究科長名にて発行しております。

Ⅱ．厚生労働科学研究費補助金の管理及び経理事務委任に対する承諾書について

本学では、「厚生労働科学研究費補助金における事務委任について」（平成13年7月5日厚科第332号厚生科学課長決定（平成29年3月31日　最新版））に基づき、補助金の管理及び経理事務について、所属機関の長の責のもと、その機関において行うこととしております。

なお当該事務について、「国立大学法人大阪大学における公的研究費の取扱いに関する規程」第6条に基づき、実質的な責任と権限を持つ者として、医学系研究科長への委任及び同研究科長よりの承諾を行っております。

Ⅲ．厚生労働科学研究費補助金の受領委任に関して

本学では、「厚生労働科学研究費補助金における事務委任を行った場合の国庫補助金の受領の委任について」（平成13年10月25日厚科第472号厚生科学課長決定（令和3年1月21日　最新版））に基づき、「国立大学法人大阪大学研究費補助金取扱要項」第6条により、補助金の受領について、所属機関の長（学長）への委任及び同長よりの承諾を行っております。

〔参考〕大阪大学規程集　https://www.osaka-u.ac.jp/jp/about/kitei/reiki_taikei/r_taikei_01_05.html

大阪大学教授会通則

（審議事項等）

第4条　教授会は、総長が次に掲げる事項について決定を行うに当たり教育研究に関する専門的な観点から意見を述べるものとする。

(1)　学生の入学、卒業及び課程の修了に関すること。
(2)　学位の授与に関すること。
(3)　教育課程の編成等に関すること。
(4)　学生の除籍及び懲戒に関すること。
(5)　教員の人事に関すること。
(6)　組織の長の選考及び解任に関すること。
(7)　称号の付与に関すること。
(8)　教育研究組織の再編に関すること。
(9)　共同研究講座等の設置に関すること。
(10)　諸規程の制定及び改廃に関すること。
(11)　概算要求に関すること。

2　教授会は、前項に規定するもののほか、総長及び学部長その他の教授会が置かれる組織の長（以下この項において「総長等」という。）がつかさどる教育研究に関する事項について審議し、及び総長等の求めに応じ、教育研究に関する専門的な観点から意見を述べることができる。

国立大学法人大阪大学における公的研究費の取扱いに関する規程　抜粋

（部局等管理責任者）

第6条　部局等（本部事務機構を含む。以下この条において同じ。）における公的研究費の運営及び管理について実質的な責任と権限を持つ者として部局等管理責任者を置き、当該部局等の長（本部事務機構にあっては、財務を担当する理事）をもって充てる。

国立大学法人大阪大学研究費補助金取扱要項　抜粋

（研究費補助金の経理事務の委任）

第６条 研究代表者等は、研究費補助金の交付内定（継続分を含む。）を受け、研究費を受領する場合は、学長にその受領を委任したものとし、経理に関する事務を所属する部局長に委任したものとみなす。
ただし、受領委任について配分機関から別途定めがある場合は、その定めにより取り扱うものとする。

令和　6年　3月　6日

厚生労働大臣
~~（国立医薬品食品衛生研究所長）~~ 殿
~~（国立保健医療科学院長）~~

機関名　国立大学法人島根大学

所属研究機関長　職　名　学長

氏　名　服部　泰直

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患政策研究事業

２．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

３．研究者名　（所属部署・職名）　医学部・教授

（氏名・フリガナ）　金﨑　啓造　・カナサキ　ケイゾウ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

厚生労働大臣　殿

令和　6年　4月　26日

機関名　聖隷佐倉市民病院

所属研究機関長　職　名　病院長

氏　名　鈴木　理志

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患対策研究事業

２．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

３．研究者名　（所属部署・職名）　聖隷佐倉市民病院　総看護部長

（氏名・フリガナ）　内田　明子（ウチダ　アキコ）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入 (※1)		
	有	無	審査済み	審査した機関	未審査 (※2)
人を対象とする生命科学･医学系研究に関する倫理指針 (※3)	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □(無の場合はその理由：　)
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □(無の場合は委託先機関：　)
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □(無の場合はその理由：　)
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

厚生労働大臣　殿

令和　6年　3月29日

機関名　茨城キリスト教大学

所属研究機関長　職　名　学長

氏　名　上　野　尚　美

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患対策研究事業

２．研究課題名　慢性腎臓病(CKD)患者に特有の健康課題に適合した多職種連携による生活・食事指導等の実証研究

３．研究者名　（所属部署・職名）　生活科学部食物健康科学科　教授

（氏名・フリガナ）　石 川　祐 一　（イシカワ ユウイチ）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入 (※1)		
	有	無	審査済み	審査した機関	未審査 (※2)
人を対象とする生命科学･医学系研究に関する倫理指針 (※3)	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

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５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由:　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関:　）
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（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

厚生労働大臣　殿

令和6年　4月　28　日

機関名　東京医科大学

所属研究機関長　職　名　学長

氏　名　林 由起子

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　腎疾患対策研究事業

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３．研究者名　（所属部署・職名）　病院　薬剤部　薬剤部長

（氏名・フリガナ）　竹内　裕紀（タケウチ　ヒロノリ）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入 (※1)		
	有	無	審査済み	審査した機関	未審査 (※2)
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研究倫理教育の受講状況	受講 ■　　未受講 □

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