We compared the prevalence of CKD between two community-based screened cohorts (Ibaraki vs. Okinawa) using standardized serum creatinine measurements and adopted a new, accurate GFR estimation formula for the screened Japanese population [16]. The CKD prevalence was higher in Okinawa than in Ibaraki, even among groups of similar age and sex. In particular the prevalence rate of a GFR <45 ml/min/1.73 m^2 was higher in Okinawa. However, as a whole, mean levels of eGFR were higher in Okinawa. These results might be explained by a rapid progression of CKD, insufficient therapy for CKD, or both.

Ethnic differences in CKD prevalence

The prevalence of CKD stages 3–5 differs among various ethnic groups [17, 18]. The CKD prevalence in Japan is one of the highest in the world [19]; this might be explained by the age of the population in Japan, as >20% of the population are 60 years and older. CKD prevalence is higher among those with hypertension and diabetes mellitus (DM). In Okinawa, however, the prevalence of CKD was higher even in those without hypertension or hyperglycemia. Okinawan people are short in stature and have a higher prevalence of low birth weight than the national average. A lower birth weight is associated with a lower nephron number and a significant risk of developing ESRD [20]. A low nephron number may result in the future development of hypertension and DM-related nephropathy [21].

Asian populations, including the Japanese, generally have low muscle mass and low protein intake, which could impair the performance of the MDRD (Modification of Diet in Renal Disease) study equation. The KDIGO work group has initiated an action to improve clinical practice by introducing GFR estimating equations that were developed for a large cohort of various racial and other groups for international comparisons. At the 2009 KDIGO Controversies Conference, a consensus that CVD mortality is independent of proteinuria and eGFR was reached [22, 23]. In Japan, measurement of microalbuminuria is not usually allowed unless incipient DM nephropathy is suspected. Dipstick proteinuria has been used for over 30 years for universal screening.

Lifestyle and CKD

Lifestyles have been changing in Japan and these changes are evident in Okinawa after the return of Okinawa to Japan in 1972. According to the current national data of MHWL in 2004, the prevalence of overweight (BMI ≥25 kg/m^2) is 32.7% in men and 17.9% in women. Interestingly, the prevalence of overweight increased in every age group in men, but not in women. Reasons for the increase in obesity are sedentary lifestyle due to the increase in use of automobiles and public transport, because the total calorie intake has apparently not increased in Japan. Salt intake remains high in Japan (12 g/day), and given the increased prevalence of obesity, further salt restriction is recommended. The smoking rate decreased less than 40% in 2005 and is decreasing slightly every year. The current smoking rate is reported to be 21.8% (36.8% in men, 9.1% in women),

Hyperuricemia has been associated with gout, CKD progression, and atherosclerosis [24]. Increased incidence of ESRD due to an unknown origin might be related to hyperuricemia and other types of chronic interstitial nephropathy. Recent animal studies support the role of hyperuricemia in the progression of CKD, but there are few randomized control trials on uricosuric drugs. Such a tendency may also be due to the frequent use of nonsteroidal anti-inflammatory drugs and antibiotics.

CKD as risk factor for CVD in the general population

Several studies have confirmed the significance of CKD on the development of CVD and mortality; the lower the eGFR, the higher the incidence of CVD [25, 26]. The cut-off levels of eGFR, however, are not yet clear. Currently, the JSN CKD Practice Guide has set the cut-off level at eGFR lower than 50 ml/min/1.73 m^2. CVD death rates might be different according to the type and severity of CVD and could be reduced by multidimensional treatments in the community. The death rates from CVD could also be dependent on the rehabilitation facility, including dietary and lifestyle modifications and drug treatment such as renin–angiotensin system inhibitors. These modalities have been available under full-coverage of the social insurance system in Japan. Recently, the number of 'non-insured' patients and/or those not able to afford medical costs has decreased the number of patients able to take renin–angiotensin system inhibitors, because the medication cost is only partially covered. The incidence of dialysis is, at least partly, related to the amount of money used for renin–angiotensin system inhibitors.

A nationwide specific health check-up and guidance system was initiated in April 2008 in Japan. The aim of this project is to detect metabolic syndrome, modify lifestyle and prevent CVD. The target population is Japanese citizens aged between 40 and 74 years of age (http://www.mhwl.go.jp). Participants are eligible with public support for standard health check such as measurements of height, weight, waist circumference, blood pressure, fasting blood glucose, hemoglobin A1c, triglyceride, serum high-density lipoprotein (HDL) cholesterol, low-density (LDL) cholesterol, GOT, GPT, gamma-GTP, hemoglobin, uric acid, serum creatinine, dipstick urine test for proteinuria,

hematuria, and glucosuria. Questionnaires for past history of stroke, cardiac disease, kidney disease, lifestyles such as smoking, alcohol intake, walking, etc., and treatment for hypertension, DM, and dyslipidemia are also performed. Proteinuria is coded as (−), (±), (1+), (2+), and (3+). Serum creatinine is measured using an enzymatic method. GFR is estimated using the Japanese formula. Reference levels for triglyceride, HDL cholesterol, LDL cholesterol, uric acid, fasting blood glucose, and hemoglobin A1c are set at 150 mg/dl, 40 mg/dl, 100 mg/dl, 7 mg/dl, 110 mg/dl, and 6.1%, respectively. Blood pressure is measured using a standard sphygmomanometer in all cohorts. Hypertension is defined as ≥140/90 mmHg or on antihypertensive medication. DM is defined as hemoglobin A1c ≥6.1% or on medication for DM.

Anonymously provided individual records for 580,000 participants in 12 communities or prefectures were included in this project. Among them, databases were obtained from Yamagata, Miyagi Fukushima, Ibaraki, Tokyo, Kanagawa, Niigata, Osaka, Okayama, Kochi, Fukuoka, and Okinawa and they were obtained after written informed consent with respective institute review boards for the ethics issues, and are currently under investigation (principal investigator: Prof. T. Watanabe).

The JSN has initiated several cohort studies using internet registration such as renal biopsy, CKD, nephritic syndrome, rapidly progressive kidney disease, etc. Within several years, outcome studies will be published through the collaboration with JSN affiliated hospitals and universities and with the JSDT.

Summary

The present study reviewed the role of CKD in CVD in the Japanese population both pre-ESRD and ESRD. CKD is an important predictor of CVD similar to other parts of the world. The effects of diet and lifestyle, however, which differ considerably in Japan from other places in the developed world, remain to be investigated. Strategies for early detection are needed as CKD remains asymptomatic until the late stages in many cases. Timely treatment for CKD is mandatory to save on costs for unnecessary care and tests. Unless CDK is properly managed, it will not be possible to maintain quality and longevity of life. The Japanese society is rapidly aging and we will have the largest proportion of elderly people in the world [27]. A life-long and systematic management program is warranted for CKD patients.

Acknowledgments Part of this manuscript was presented at the KDIGO Controversies Conference, October 2010, in London. No financial support was obtained from any institution or company.

Conflict of interest None.

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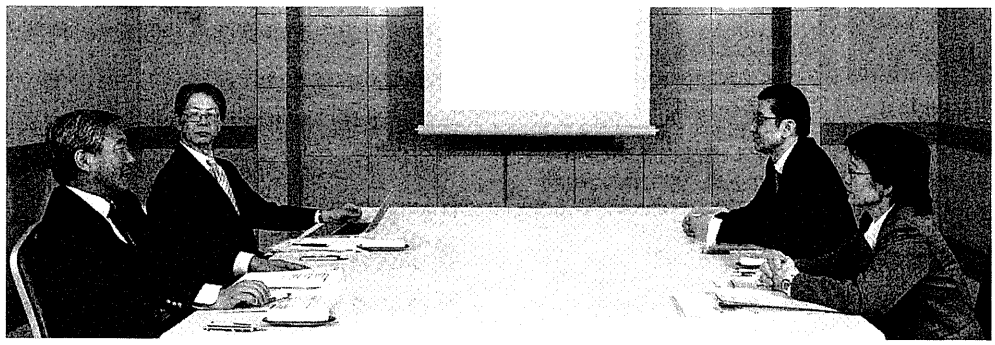
《座談会》

これからの静岡県のCKD治療戦略を考える



◆出席者<発言順>
藤垣　嘉秀（浜松医科大学 内科学第一講座）【司会】
米村　克彦（富士宮市立病院 内科）
森　　典子（静岡県立病院機構 静岡県立総合病院 腎臓内科）
磯﨑　泰介（社会福祉法人 聖隷福祉事業団 総合病院 聖隷浜松病院 腎臓内科/腎センター）

藤垣◆本日は，静岡県東部，中部，西部の基幹病院の腎臓内科の先生にお集まりいただき，CKD早期発見/治療を達成するための問題点，とくに腎専門医と一般内科医との認識の違いを議論することで，これからの静岡県におけるCKD治療戦略を考えたいと思います．

従来，慢性の経過をたどる腎疾患は治療法のないものとして考えられていましたが，早期発見/診断により，進行の抑制から臨床的寛解まで期待できることがわかり，その患者数の多さ，末期腎不全への進展，そして心血管イベントの合併抑制という観点から，CKDへの対策が全世界的に叫ばれています．

わが国では，かかりつけ医と腎専門医の病診連携によるCKD対策促進のために，2007年9月にCKD診療ガイドが出版され，CKDの概念はかなり定着したものと思われます．CKD治療においては，地域単位での対策と実践が最重要と考えられますので，かかりつけ医と腎専門医の連携は欠かせません．

CKDの早期発見のために

藤垣◆CKDとは，蛋白尿などの腎障害の存在を示す所見，もしくは，糸球体濾過量（GFR）60 ml/min/1.73 m^2未満の状態が3ヵ月以上持続する状態と定義されます．また，GFRのレベルによるCKD病期分類がなされ，病期ごとの対策が推奨されています．

CKDの診断と管理・治療のための検査オーダーの必須項目として，尿試験紙法による尿蛋白定性と尿潜血反応，随時尿における尿蛋白定量とクレアチニン（Cr）定量，そして血清Cr値があります．腎専門医と一般内科医ではCKD早期発見のための認識に違いがあると思いますが，CKD診断の検査項目と実施状況，そしてCKD診断検査実施のタイミング，また，eGFR算出の重要性の認識などについて，各地区での実情やご意見をうかがいたいと思います．はじめに，静岡東部地区の米村先生，こ

【藤垣嘉秀先生】

浜松医科大学 内科学第一講座
准教授

ふじがき・よしひで
1984年　浜松医科大学卒業
1984年　浜松医科大学第一内科入局
1991年　浜松医科大学大学院博士課程修了
1992年　フライブルク大学医学微生物衛生研究所・免疫部門・フンボルト財団奨学研究員
1996年　浜松医科大学医学部内科学第一講座 助手
2007年　浜松医科大学附属病院第一内科講師
2010年より現職
研究テーマ：急性腎不全の予防および尿細管細胞再生

の点に関していかがでしょうか.

米村◆一般の先生方のなかには，今までの慢性腎不全がCKDという名称に変わったという認識しかなく，CKDが動脈硬化性疾患のリスクであるということをあまり認識されていない方も多いのではないでしょうか．一般の先生方におけるCrや検尿の検査項目や実施状況はわかりませんから，潜在的なCKD患者数も正確に把握できていないと思います.

藤垣◆中部地区の森先生，いかがでしょう.

森◆一般内科を受診されていて，腎機能が低下している患者さんを人間ドックの先生が見つけ出し，当院に紹介してくれていますが，それはCKD患者全体の氷山の一角で，われわれはその氷山の一角を診療しているにすぎないと考えています．やはりCKDの患者数にはかなり目こぼしがあるのではないでしょうか.

ただ，CKDのキャンペーンによって，周知度は上がっていると思います．静岡地区で送られてくる患者さんのデータはほとんどeGFRが算出してありますので，一般内科医の先生方の更なるCKDへの理解が重要になると思います.

藤垣◆県西部の磯﨑先生，いかがでしょうか.

磯﨑◆CKDの定義からもわかるように，腎障害の所見がある群，eGFRが低下し慢性腎不全の状態となった群，それぞれをわれわれは相手にしています．検尿異常やCrの軽度上昇の所見で，早期介入をおこなうことでステージの進行を根本的に阻止できる症例が，現在のCKDでは周知徹底されていない可能性があり，われわれ腎臓内科医も注意する必要があります.

CKD診療ガイドでは蛋白尿2+以上または尿潜血・尿蛋白がともに1+以上で専門医への紹介を推奨していますが（**図1**）[1]，1999年からの11年間での腎生検327例を解析したところ，後者の紹介は比率として多くはありません．つまり，慢性腎炎で遭遇する頻度が最も高いIgA腎症の発見は少し遅れている印象を受けます.

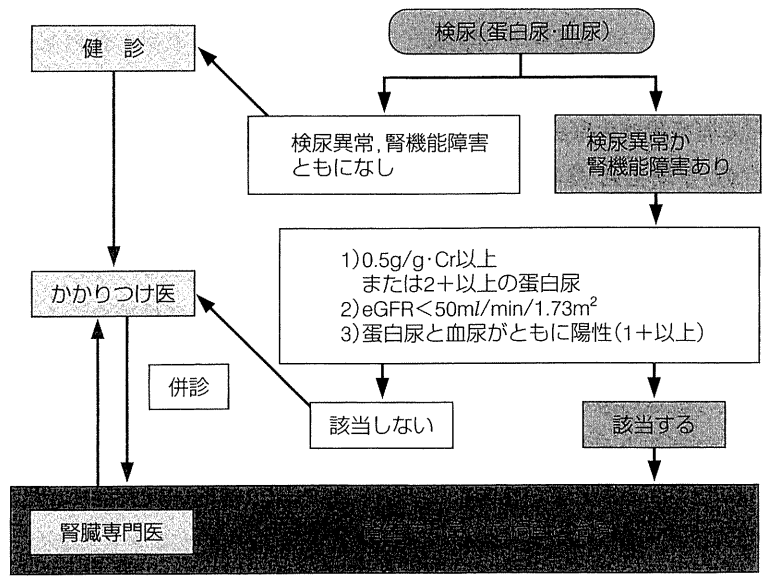


図 1. CKDの診療連携システム案
（日本腎臓学会編，2009[1]より引用）

藤垣◆eGFRは，各検査会社，基幹病院内の検査室など，かなりのところで自動的に算出し報告されていますが，問題はそれを一般内科医の方が認識されているかということです．さらに，CKDの対策にあたり尿蛋白/Cr比という概念が導入されているわけですが，CKDの検査値に対する一般内科医の認識はいかがでしょうか．

米村◆eGFRに関しては先生方によって温度差があります．ただし，eGFRには問題点もあり，高齢者で筋肉量の少ない人は高値を示し，筋肉量のある若い人では低めになるなど筋肉量による影響を受けます．eGFRは指標として現時点では最も簡便な方法だと思いますが，やはり完全なものではないので，それ以外の方法も考慮するべきだろうと思います．たとえば当院では全例24時間蓄尿をし，クレアチニン・クリアランス（CCr）を算出しています．

また，開業の先生方は蛋白尿のCr比の概念をあまりご存じないようで，尿蛋白2+や3+という状態で紹介されてくる患者さんが非常に多いですね．

森◆私の施設でもやはり尿蛋白/Cr比の概念なしで患者さんを紹介されることが多いです．当院の病診連携のチャート中には，随時のCr定量と蛋白の定量を書く項目を作ってあるのですが，連携のなかで開業医の先生に尿蛋白/Cr比の重要性を認識していただきたいと考えています．

磯﨑◆私は紹介状で「次回は蓄尿してCCrをみます」とか「蛋白尿をみさせていただき，0.5 g/g·Cr以上あれば腎生検しますよ」とお伝えすることで，そのかかりつけ医にCKD診断の道筋を示すことができればと考えています．また，当院では「腎臓いきいき手帳」というものを作り，それに蓄尿も含めたすべてのデータを記載し，かかりつけ医の先生との連携パスのかわりに使用しています．これは，実際にeGFRと蓄尿のCCrを併記することによって，その違いに注目してもらうことを目的としています．

CKD治療における実践的な病診連携のあり方

藤垣◆さて，わが国の成人人口におけるCKD患者数は約1,330万人と推計され，この数多い患者さんを的確に診療していくためには，かかりつけ医と腎専門医との病診連携が欠かせません．ここでは腎専門医への紹介タイミングや腎専門医の立場からの実践的な病診連携についてのご意見をうかがいたいと思います．まず森先生のご施設での病診連携についてはいかがでしょうか．

森◆基本的には，CKD診療ガイドに沿った形の連携をめざしていますが，ご高齢の方ではeGFR 50 m*l*/min/1.73 m^2以下ですと，ほとんどが紹介の適応となってしまい，大変なことになります．しかし，eGFR 30 m*l*/min/1.73 m^2以下ですと心疾患などの合併症が非常に多くなりますので，eGFR 40 m*l*/min/1.73 m^2以下での紹介をお願いしています．実際，当院に紹介される患者さんでは悪性腫瘍を含め合併症が多く見つかります．その後ずっと病診連携でフォローするかどうかは各症例に応じて決定しています．

藤垣◆CKDの患者さんを腎専門医に紹介するタイミングを計る指標として，半数以上の一般内科医がeGFRをあげています（**図2**）[2]．しかし，CKDの基準をeGFR60m*l*/min/1.73 m^2以下としますと高齢者のCKDは膨大な数になりますから，ここ1年間世界の趨勢をみても，高齢者のeGFRの判断基準をどうするかは議論の的になっています．

磯﨑先生はかかりつけ医の先生との病診連携，院内連

【米村克彦先生】

富士宮市立病院 院長/内科

よねむら・かつひこ
1980年　浜松医科大学医学部卒業
1980年　浜松医科大学医学部附属病院第一内科 医員（研修医）
1981年　聖隷三方原病院内科
1982年　浜松医科大学医学部附属病院第一内科 医員
1986年　米国国立衛生研究所（NIH）Visiting Fellow
1988年　浜松医科大学医学部附属病院第一内科 医員
1988年　浜松労災病院内科 医長
1990年　浜松労災病院内科副部長
1993年　浜松医科大学医学部内科学第一 助手
1998年　浜松医科大学医学部附属病院第一内科 講師
1998年　浜松医科大学医学部附属病院血液浄化療法部 助教授
2005年　富士宮市立病院 副院長
2010年より現職
研究テーマ：内科学，腎臓病学（水・電解質代謝異常，骨代謝，急性・慢性腎不全など）

【森　典子先生】

静岡県立病院機構 静岡県立総合病院 副院長/腎臓内科 主任医長

もり・のりこ
1980年　大阪大学医学部卒業
1980年　浜松医科大学 産婦人科学教室入局
1983年　静岡県立総合病院 循環器科医員
1991年　同 腎臓内科医長
2000年　同 腎センター長 兼務
2003年　同 臨床工学室長 兼務
2009年より現職
研究テーマ：CKDの病診連携，腎移植

携ともに積極的にやっておられますが，その点に関していかがでしょうか．

磯﨑◆浜松市の医師会は連携に非常に積極的で，2007年から浜松医科大学の第一内科と急性期病院である当院と医師会の3者で，CKD浜松地区病診連携委員会を立ち上げました．浜松地区のかかりつけ医のうち，当院では約40%の200人くらいの先生と連携しています．

この11年間で，連携先，紹介患者数ともに大幅に増加していますが，専門医の人数はほとんど変わりませんから紹介の患者さんを全部引き受けることは困難です．そこで当院ではスクリーニング，生活習慣指導，処方薬などを決めた後，相当数の患者さんを逆紹介しています．そして当院では定期的に，生活習慣指導や検査をフォローアップして，双方向的連携をおこなっています．

また，腎機能の低下とともに，腎専門医への来院の期間を短くすることで，患者さんへも病態の進行度を理解していただいています．腎機能が2割を切るCKDステージ4から5への移行段階では，腎専門医が透析導入を考慮し，患者さんと相談しながら治療をおこなうことで透析導入に向けて心と体の準備をしながら，円滑に透析導入していくシステムを作っています．

藤垣◆従来，専門医とかかりつけ医の双方向連携という考え方はなかったかと思いますが，森先生のご施設ではいかがですか．

森◆当院では，原則全例紹介制の外来ですので，今はかかりつけ医の先生を主体にする患者さんがほとんどです．専門医では専門医でしかできないことをしてお返しするというスタンスで，患者さんにもご理解いただいています．

かかりつけ医の先生が連携によってCKD診療への理解を深め，実臨床に活かすことができればよいのですが，

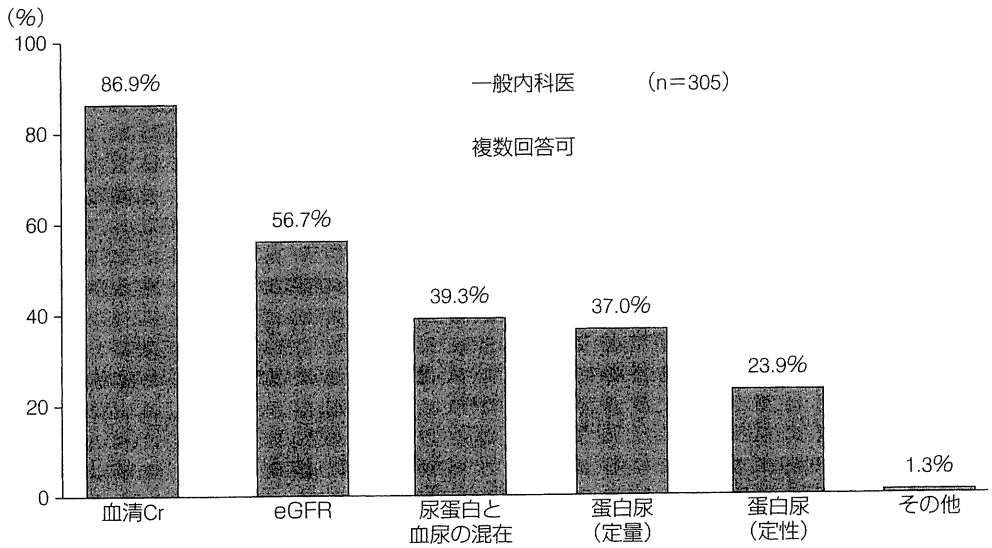


図 2. CKD患者を腎専門医に紹介する際に参考にする指標
対象：一般内科医（「内科」を第一標榜とし，20床未満の医療機関に勤務し，かつ高血圧症症例を月10例以上診察している医師）
腎専門医（腎臓内科を第一標榜とし，かつ透析患者が全症例の半分以下である医師）
（槇野博史，2010[2]より引用）

実際は症例ごとに患者さんの背景は異なりますのでなかなかむずかしいかと思います．ですので，私の場合処方や検査について毎回具体的にお願いをしています．多少，手間がかかりますが，医師会の先生方の腎臓診療に対する理解度や知識を向上していただくための，基幹病院の宿命として多少の負担はいたし方ないと思います．

藤垣◆かかりつけ医の先生および患者さん双方がメリットを感じるような病診連携のあり方というのが必要であるということですね．

【磯﨑泰介先生】

社会福祉法人 聖隷福祉事業団
総合病院 聖隷浜松病院 腎臓内科 部長/腎センター長

いそざき・たいすけ
1984年　浜松医科大学 卒業
1987年　国立循環器センター研究所 勤務
1991年　米国エモリー大学 留学
1999年　聖隷浜松病院 勤務
2009年　浜松医科大学 臨床教授
2009年　聖隷クリストファー大学 臨床教授
研究テーマ：腎疾患一般，糖尿病性腎症，血液浄化療法，臨床栄養学

高血圧合併CKDの降圧治療

藤垣◆高血圧はCKDの原因かつ増悪因子ですので，CKD治療の中心は降圧療法です．高血圧合併CKD診療では，厳格な降圧目標として130/80 mmHg未満が設定され，第一選択薬にレニン・アンジオテンシン（RA）系抑制薬の使用が推奨されています．また，多くの場合多剤併用が必要となること，降圧と同時に蛋白尿の減少をめざすことが基本とされています．

RA系抑制薬によるCKD進行抑制は蛋白尿減少効果に依存するとされ，尿蛋白減少が十分でない場合には最大投与量までの増量が推奨されています．実際ロサルタンでは，50 mgから100 mgへ増量することで，降圧に関係なく尿中アルブミンの更なる減少が報告されています[3]．

一方，RA系抑制薬への追加薬として，第二選択薬はCa拮抗薬と利尿薬が推奨されています（**図3**）[4]．たとえばGFR30ml/min以上ある場合にサイアザイド系利尿薬を処方することで，ナトリウム（Na）再吸収抑制，循環血液量の減少，末梢血管抵抗の減少による降圧が期待されます．副作用としての低カリウム（K）血症，耐糖能低下，高尿酸血症は，少量の利尿薬であればあまり問題にならないとのデータもあります．

CKDやその背景疾患であるメタボリックシンドローム，糖尿病，高齢の患者では，食塩感受性が高く，RA系抑制薬と利尿薬の併用は理にかなっているといえ，夜間高血圧を改善する効果も認められています．さらに，2

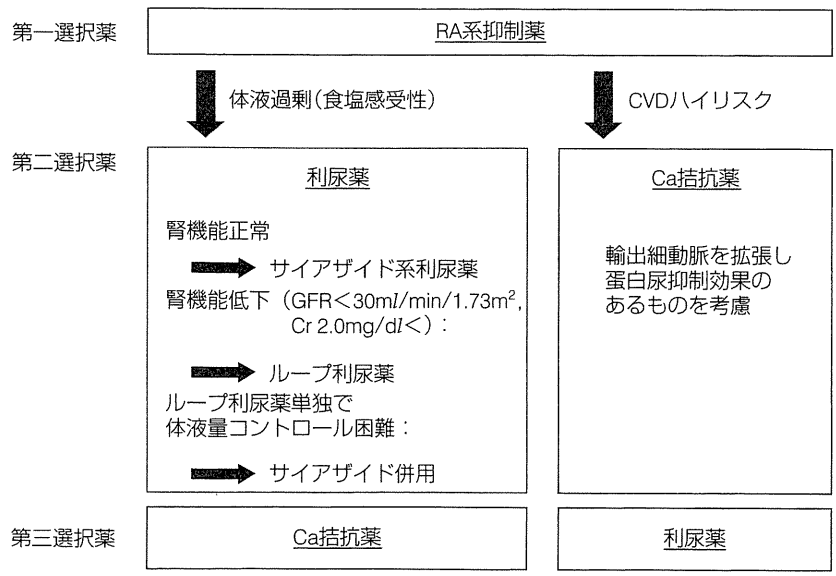


図3. CKDの高血圧治療の進め方
（日本腎臓学会・日本高血圧学会編，「CKD診療ガイド高血圧編」[4]より引用）

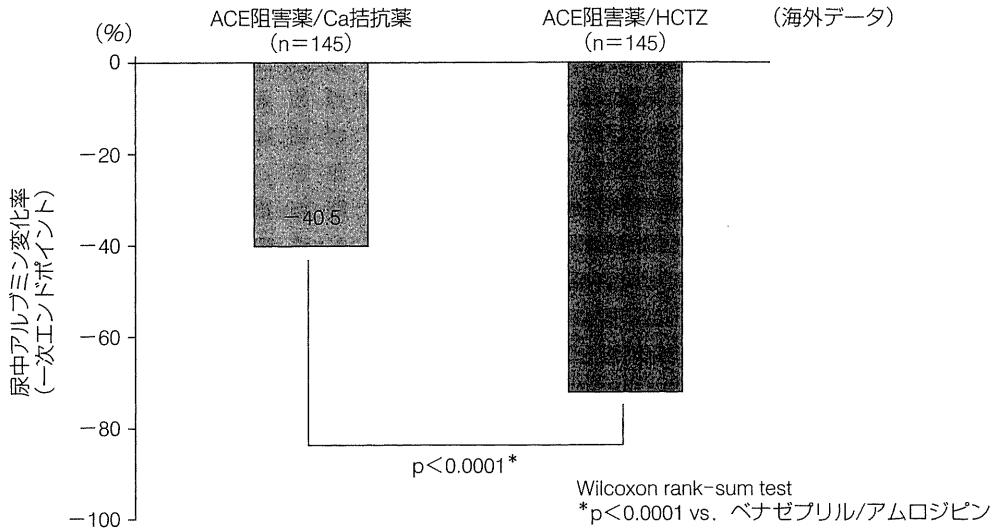


図 4. RA 系抑制薬/利尿薬による腎保護効果
対象：2 型糖尿病を合併した高血圧症患者 294 例
方法：ベナゼプリル 20 mg/アムロジピン 5 mg またはベナゼプリル 20 mg/ヒドロクロロチアジド（HCTZ）12.5 mg から治療を開始し，130/80 mmHg に達しない場合は増量，または他の降圧薬を追加し 52 週間投与した．
一次エンドポイント：尿中アルブミン/Cr 比，降圧効果，アルブミン尿の正常化
（Bakris GL *et al*, 2008[5]より引用）

型糖尿病を合併しアルブミン尿を有する高血圧患者を対象とした GUARD 試験（Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension）では，RA 系抑制薬と少量利尿薬を長期間投与することにより，腎障害の指標である尿中アルブミン量の約 72% の低下がみられています．アルブミン尿の減少効果は，RA 系抑制薬と少量利尿薬併用群で，Ca 拮抗薬アムロジピン併用群よりも有意に大きく，腎保護効果がすぐれる可能性が示唆されています（**図 4**）[5]．

近年，利尿薬の有用性の再認識とともに，ARB と利尿薬との配合剤が使用できるようになりましたが，高血圧合併 CKD の治療における RA 系抑制薬の増量，利尿薬・Ca 拮抗薬を追加すべきケースなどについて先生方のご意見をお願いしたいと思います．

米村◆ARB は CKD 治療の第一選択薬として勧められていますが，使用には二つの条件があると私は考えています．血清 K が 4.8 mEq/*l* 以下であるということが一つ．もう一つは，紹介された患者さんや，腎機能の悪い患者さんに対しては必ず CT で腎臓のボリュームや，下部尿路，腎動脈起始部の石灰化を確認し，狭窄の有無をしっかりみるということです．

藤垣◆K の値ですと，かかりつけ医の先生も測定すればすぐにわかるということですが，その他の項目に関しては，なかなか見極めがむずかしいと思います．そのへんはかなりハードルが高いですね．磯﨑先生はいかがでしょうか．

磯﨑◆当院では CT まではやっておりませんが，初診で全例にエコーをおこない狭窄がなければ，RA 系はファーストチョイスで使います．また，K の値ももちろん考慮しますが，K が上がった場合，消化管出血やアシドーシスなど薬以外で K を上げる要因の有無を判断したうえで，食事療法で K 制限をかけるなどしてできるだけ RA 系抑制薬を続行するようにします．

藤垣◆森先生のご施設では，どのような治療をされていますか．

森◆当院にいらっしゃるのは全例紹介患者さんですし，人間ドックからいらっしゃる患者さんもかかりつけ医をもっておりますので，すでに RA 系抑制薬が処方されていることが多いです．ですから，われわれのところではそちらを増量するか，あるいは Ca 拮抗薬か利尿薬を併用するかというところを判断して，かかりつけ医の先生にお返しするような形になっています．

藤垣◆先生のところでは，蛋白尿を減らすために，血圧に関係なくARBを増量することはありますか．

森◆しばしばありますね．

藤垣◆高食塩摂取の状態では，血圧だけではなく内皮細胞障害への影響なども示唆されていますね．CKD治療には長期のフォローアップが必要であり，厳格に降圧することが重要であると考えられます．磯﨑先生，どうでしょうか．

磯﨑◆2004年に，当科を外来受診している糖尿病性腎症60人の血圧と食塩感受性を調べました．収縮期血圧を130～140 mmHgにコントロールするのに必要な降圧薬の平均投与数は2.4剤でした．糖尿病性腎症ではとくに，血圧のコントロールに難渋することが多いといえます．

その方々の蓄尿を調べますと，収縮期血圧と食塩摂取量にはきれいな相関関係がみられ，食塩感受性による収縮期血圧への影響は明らかでした．したがって，利尿薬によるNaの排出は有用であると考えられます．また，糖尿病性腎症では，インスリン抵抗性や浮腫を伴うことが非常に多く，こうした例では少量の利尿薬を積極的に使用する必要があります．

藤垣◆CKD合併高血圧では処方される降圧薬の種類が多い傾向にありますが，ARB/HCTZの合剤も臨床で使用できるようになっています．CKDでは降圧薬以外の薬剤も多く処方されており，薬剤数が減ることによる服薬コンプライアンスの向上というメリットなども考えられます．CKD患者さんに合剤を使用する場合，留意すべき点はございますか．

森◆合剤への切り替えの際には，残薬をおもちの患者さんの場合，前の薬剤と一緒に服用してしまう可能性もあるので注意が必要ですね．

磯﨑◆とくに腎専門医では，ステージが進んで体液管理・血圧管理がむずかしい患者さんを相手にすることが多く，調節することが多いので合剤の処方は慎重になると思います．ただし，かかりつけ医レベルでは，ステージが比較的若く腎機能も比較的予備力がある人を診察されることが多いので，剤数を増やすことなくそういう方の治療ができるという点がメリットだと考えます．

そのうえで，先ほどの季節性の問題や摂食量，体液量を考慮して，臨機応変な処方が必要になるのではないでしょうか．専門医とかかりつけ医の先生で密な連携をすることが大事だと考えます．

藤垣◆そうですね．合剤に関しては，われわれ腎専門医もその効果的な使い方を考える必要があるということでしょうか．

本日は，基幹病院の腎臓内科の立場から，静岡各地，施設の事情なども交えて議論していただきました．

基本的には，どの場所で発生したCKD患者さんも，今ある医療を平等に受けることができるということが，われわれの願いかと思います．本日の議論が，静岡県でのCKD対策をどのように考えるかということのきっかけとなれば幸いです．本日はどうもありがとうございました．

（2010年10月　静岡）

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Clin Exp Nephrol (2011) 15:248–257
DOI 10.1007/s10157-010-0396-7

ORIGINAL ARTICLE

Management of anemia in chronic kidney disease patients: baseline findings from Chronic Kidney Disease Japan Cohort Study

Tadao Akizawa · Hirofumi Makino · Seiichi Matsuo · Tsuyoshi Watanabe · Enyu Imai · Kosaku Nitta · Yasuo Ohashi · Akira Hishida · Chronic Kidney Disease Japan Cohort Study Group

Received: 4 October 2010 / Accepted: 13 December 2010 / Published online: 15 January 2011

Abstract
Background Anemia is a factor that affects the outcome of patients with chronic kidney disease (CKD); however, there are only a few reports on the management of anemia in Japanese patients with CKD who are not on dialysis.
Methods We investigated the prevalence, related factors and management of anemia in CKD stage 3–5 patients in Japan based on the baseline data obtained from a prospective cohort study (Chronic Kidney Disease Japan Cohort). Anemia was defined as having a hemoglobin (Hb) level of <11 g/dL or receiving erythropoiesis stimulating agent (ESA) therapy.
Results The result indicated that 946 out of 2,930 patients had anemia. Of these 946 patients, 385 were receiving ESA treatment for anemia and had an Hb level of 10.28 ± 1.19 g/dL (mean ± SD). The percentage of these patients with an Hb level above the target of 11 g/dL proposed for treatment by the Japanese guidelines, and above the maintenance level of 10 g/dL approved for ESA therapy in Japan, was only 30.1 and 61.6%, respectively. In contrast, the percentage of patients receiving no ESA therapy was 67.6 and 55.7%, respectively, among those with an Hb level of <11 and <10 g/dL.
Conclusions These data suggested that prevalence of anemia was high in Japanese patients with CKD stage 3–5, that the percentage of patients receiving ESA was low among those who required ESA, and that a large number of patients receiving ESA failed to maintain the recommended level of Hb.

Keywords CKD · Erythropoiesis stimulating agent (ESA) · Hemoglobin (Hb) · Anemia

T. Akizawa (✉)
Division of Nephrology, Department of Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
e-mail: akizawa@med.showa-u.ac.jp

H. Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

S. Matsuo · E. Imai
Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

T. Watanabe
The Third Department of Internal Medicine, Fukushima Medical College, Fukushima, Japan

K. Nitta
Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

Y. Ohashi
Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo, Japan

A. Hishida
First Department of Medicine, Hamamatsu University School of Medicine, Shizuoka, Japan

Introduction

The number of incident patients with end-stage renal disease (ESRD) in Japan is increasing annually. Excluding dialysis and kidney transplant patients, approximately 10% or more of the general population reportedly suffer from stage 3 or more advanced CKD. In particular, reports indicated that the number of people in Japan with positive proteinuria or an estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73 m^2, who were at a higher risk for worsening renal function or emergence of cardiovascular disease (CVD),

was approaching six million [1]. Although anemia is a factor that affects the outcome of CKD patients, there have been few large-scale clinical studies investigating the effects of anemia in CKD patients in Japan.

The Chronic Kidney Disease Japan Cohort (CKD-JAC) study is the first large-scale prospective observational study in pre-dialysis patients in Japan. We analyzed the baseline data on the management of anemia to evaluate the prevalence and factors associated with anemia as well as the current practice of anemia treatment with a focus on erythropoiesis stimulating agents (ESA).

Subjects and methods

Study subjects were outpatients with CKD who were enrolled between April 2007 and December 2008 in the CKD-JAC study in 17 large-scale hospitals throughout Japan. The inclusion and exclusion criteria for enrollment are described elsewhere [2].

In this paper we describe baseline data from patients with anemia, defined as having an Hb level of <11 g/dL, or receiving ESA therapy, for which epoetin alfa and beta were the only preparations available at the time of enrollment. In addition, diabetes patients were defined as those with diabetic nephropathy as the primary cause of CKD, with a diabetes complication, undergoing treatment with a diabetes drug or having an HbA1c of >6.5%. Diabetic nephropathy was classified by the medical judgment provided on each patient's medical record. A descriptive analysis of continuous and categorical variables was performed. Continuous variables are presented as means, medians, standard deviations and ranges, and categorical variables are presented as proportions. Comparisons were made by means of t test or chi-square test, as appropriate. Plots of eGFR versus Hb level, along with coefficient of variation (R^2) and corresponding P derived from the linear regression analysis, were generated. Statistical analyses included logistic regression analysis to determine odd ratios for assessing patient characteristics that had an effect on anemia and ESA therapy. A stepwise selection process was then used for developing multivariate logistic regression models, in which all independent variables with univariate associations of P of 0.10 or less were allowed to enter the model. The two-sided level of significance was set at 5%.

Results

Subjects and their characteristics

Of the total 2,977 enrolled patients eligible for follow-up observation, 2,930 patients whose Hb values were documented at study initiation were analyzed for anemia management (Table 1). Out of 2,930 subjects, 946 (32.3%) met the definition of anemia (Table 2).

Distribution of patients with anemia

The relationship between eGFR and Hb level is shown in Figs. 1 and 2. eGFR and Hb level were in a positive correlation ($R^2 = 0.2294$; $P < 0.0001$), and the percentage of patients having an Hb level of <11 g/dL increased as eGFR declined.

Table 3 shows the distribution of patients with anemia by eGFR. A breakdown by eGFR (10.4% with an eGFR of >45 mL/min/1.73 m^2; 15.1% with 30 to <45 mL/min/1.73 m^2; 38.3% with 15 to <30 mL/min/1.73 m^2; and 68.4% with <15 mL/min/1.73 m^2) indicated a rise in the percentage of patients with anemia associated with a decline in renal function ($P < 0.0001$).

Figure 3 shows the percentage of patients with anemia by eGFR among diabetics and nondiabetics. The prevalence of anemia was higher in diabetic patients compared with nondiabetic patients ($P < 0.0001$). In the group of patients with an eGFR of >45 mL/min/1.73 m^2, the prevalence more than doubled from 7.5% among nondiabetics to 16.7% among diabetics. The prevalence of anemia also increased from 64.3% among nondiabetics to 73.9% among diabetic patients and to 82.7% among those with diabetic nephropathy as the primary disease in the group with an eGFR of <15 mL/min/1.73 m^2.

Treatment for anemia

The percentage of patients on ESA (epoetin alfa or beta) therapy was 13.1% (385 of 2,930) of the entire study group or 40.7% (385 of 946) of the group of patients with anemia. Of the 946 patients with anemia, 158 (16.7%) were receiving iron therapy.

Figure 4 shows the percentage of patients undergoing such therapy by Hb level. The percentage of patients receiving anemia treatment increased as the Hb level declined ($P < 0.0001$). The number of patients concomitantly placed on ESA plus iron therapy, however, was less than the number of those on ESA therapy alone across all Hb levels. Among 830 patients with an Hb level of <11 g/dL, the number of patients on ESA therapy was 269 (32.4%), with only 71 (8.6%) concomitantly receiving ESA and iron therapy. In the group of 334 patients with an Hb level of <10 g/dL, which is the level for treatment initiation according to the package insert of the current ESA preparation, 148 (44.3%) were undergoing ESA therapy.

The percentage of patients receiving ESA therapy by eGFR indicates that the earlier the stage of CKD, the lower the percentage of patients receiving ESA to treat anemia

Table 1 Patient characteristics classified by anemia

Variable	Total (n = 2,930)	Anemia[a] (n = 946)	Without anemia (n = 1,984)	P value
Sex [n (%)]				
Female	1,111 (37.9)	472 (49.9)	639 (32.2)	<0.0001
Male	1,819 (62.1)	474 (50.1)	1,345 (67.8)	
Age (year)				
Mean (SD)	60.9 (11.5)	62.7 (11.2)	60.0 (11.6)	<0.0001
Median (min–max)	63.0 (22–77)	66.0 (22–77)	62.0 (22–77)	
1Q–3Q	55.0–70.0	58.0–71.0	53.0–69.0	
Causative diseases of CKD [n (%)]				
Diabetic nephropathy	608 (20.8)	292 (30.9)	316 (15.9)	<0.0001
Glomerulonephritis	1,125 (38.4)	307 (32.5)	818 (41.2)	<0.0001
Secondary glomerulonephritis/vasculitides	86 (2.9)	28 (3.0)	58 (2.9)	0.9564
Interstitial nephritis/pyelonephritis	167 (5.7)	35 (3.7)	132 (6.7)	0.0013
Hypertension/large vessel disease	539 (18.4)	154 (16.3)	385 (19.4)	0.0411
Cystic/hereditary/congenital diseases	38 (1.3)	12 (1.3)	26 (1.3)	0.9252
Neoplasms/tumors	17 (0.6)	9 (1.0)	8 (0.4)	0.0678
Miscellaneous conditions	350 (11.9)	109 (11.5)	241 (12.1)	0.6257
Medical history [n (%)]				
Hypertension	2,391 (81.6)	796 (84.1)	1,595 (80.4)	0.0143
Myocardial infarction	146 (5.0)	47 (5.0)	99 (5.0)	0.9799
Angina	251 (8.6)	93 (9.8)	158 (8.0)	0.0913
Congestive heart failure	114 (3.9)	48 (5.1)	66 (3.3)	0.0222
ASO	107 (3.7)	48 (5.1)	59 (3.0)	0.0046
Stroke	340 (11.6)	119 (12.6)	221 (11.1)	0.2551
Diabetes	1,109 (37.8)	435 (46.0)	674 (34.0)	<0.0001
Cancer	213 (7.3)	64 (6.8)	149 (7.5)	0.4678
Diastolic blood pressure (mmHg)[b]				
Mean (SD)	76.2 (11.9)	73.0 (11.9)	77.8 (11.5)	<0.0001
Median (min–max)	76.0 (33–128)	73.7 (33–116)	78.0 (35–128)	
1Q–3Q	68.7–84.0	65.3–81.0	70.0–85.0	
Systolic blood pressure (mmHg)[b]				
Mean (SD)	131.7 (18.6)	132.2 (19.4)	131.4 (18.2)	0.2803
Median (min–max)	130.7 (68–235)	130.8 (73–218)	130.3 (68–235)	
1Q–3Q	119.7–142.7	120.0–144.0	119.5–142.0	
BMI				
Mean (SD)	23.51 (3.81)	22.50 (3.61)	23.99 (3.80)	<0.0001
Median (min–max)	23.16 (10.3–39.8)	22.22 (10.3–36.0)	23.71 (12.1–39.8)	
1Q–3Q	20.96–25.74	20.13–24.64	21.45–26.22	
<25	1,816 (62.0)	662 (70.0)	1,154 (58.2)	<0.0001
≥25 to <30	684 (23.3)	169 (17.9)	515 (26.0)	
30≤	145 (4.9)	26 (2.7)	119 (6.0)	
Serum Cr (mg/dL)				
Mean (SD)	2.16 (1.06)	2.72 (1.23)	1.89 (0.85)	<0.0001
Median (min–max)	1.83 (0.7–8.4)	2.50 (0.8–8.4)	1.64 (0.7–8.0)	
1Q–3Q	1.38–2.63	1.76–3.49	1.31–2.18	
eGFR (mL/min/1.73 m^2)				
Mean (SD)	28.66 (12.23)	21.35 (10.47)	32.15 (11.45)	<0.0001
Median (min–max)	27.96 (5.4–73.6)	19.00 (5.4–61.9)	32.55 (6.4–73.6)	
1Q–3Q	18.63–37.64	12.91–26.81	23.11–40.47	

Table 1 continued

Variable	Total (n = 2,930)	Anemia[a] (n = 946)	Without anemia (n = 1,984)	P value
Uric protein (g/day)[c]				
Mean (SD)	1.347 (2.010)	1.761 (2.647)	1.153 (1.593)	<0.0001
Median (min–max)	0.690 (0.00–28.08)	0.851 (0.00–28.08)	0.600 (0.00–12.83)	
1Q–3Q	0.210–1.677	0.285–2.226	0.170–1.460	
HbA1c (%)				
Mean (SD)	5.93 (0.91)	5.94 (0.90)	5.92 (0.92)	0.6519
Median (min–max)	5.70 (4.1–11.7)	5.70 (4.2–10.1)	5.70 (4.1–11.7)	
1Q–3Q	5.30–6.20	5.30–6.30	5.30–6.20	
Uric albumin (mg/g Cr)				
Mean (SD)	981.14 (1,347.01)	1,262.46 (1,545.78)	845.38 (1,217.16)	<0.0001
Median (min–max)	481.60 (2.5–14,168.2)	726.50 (4.8–9,605.1)	393.40 (2.5–14,168.2)	
1Q–3Q	121.50–1,298.60	216.35–1,684.60	90.90–1,089.90	
Ca (mEq/L)				
Mean (SD)	9.00 (0.53)	8.77 (0.59)	9.11 (0.46)	<0.0001
Median (min–max)	9.00 (5.4–11.6)	8.80 (5.4–10.6)	9.10 (6.4–11.6)	
1Q–3Q	8.70–9.30	8.40–9.20	8.80–9.40	
P (mg/dL)				
Mean (SD)	3.53 (0.70)	3.86 (0.76)	3.37 (0.60)	<0.0001
Median (min–max)	3.50 (1.6–8.6)	3.80 (1.7–8.6)	3.40 (1.6–5.8)	
1Q–3Q	3.10–3.90	3.40–4.30	3.00–3.80	
iPTH (pg/mL)				
Mean (SD)	106.0 (92.0)	144.0 (123.4)	87.8 (64.9)	<0.0001
Median (min–max)	79.0 (5–1,540)	108.5 (13–1,540)	72.0 (5–1,020)	
1Q–3Q	54.0–126.0	67.0–179.0	50.0–104.0	
CRP (mg/dL)				
Mean (SD)	0.263 (0.833)	0.337 (1.174)	0.227 (0.594)	0.0031
Median (min–max)	0.100 (0.00–23.08)	0.085 (0.00–23.08)	0.100 (0.00–11.99)	
1Q–3Q	0.040–0.200	0.040–0.200	0.040–0.200	
RBC ($\times 10^4/\mu L$)				
Mean (SD)	389.2 (62.0)	333.0 (47.4)	415.9 (48.8)	<0.0001
Median (min–max)	386.0 (107–940)	333.0 (107–940)	410.0 (252–599)	
1Q–3Q	347.0–428.0	307.0–355.0	380.0–446.0	
Hb (g/dL)				
Mean (SD)	12.06 (1.84)	10.16 (0.97)	12.97 (1.42)	<0.0001
Median (min–max)	11.90 (5.2–19.7)	10.30 (5.2–13.2)	12.70 (11.0–19.7)	
1Q–3Q	10.80–13.20	9.60–10.80	11.80–13.85	
Ht (%)				
Mean (SD)	36.15 (5.24)	30.86 (3.01)	38.68 (4.05)	<0.0001
Median (min–max)	35.85 (17.4–55.2)	31.20 (17.4–41.3)	38.00 (25.6–55.2)	
1Q–3Q	32.60–39.55	29.20–32.70	35.60–41.20	
MCV (fL)				
Mean (SD)	93.22 (5.13)	93.27 (5.87)	93.20 (4.75)	0.7391
Median (min–max)	93.00 (63.6–125.9)	93.20 (64.0–125.9)	93.00 (63.6–116.1)	
1Q–3Q	90.00–96.20	89.60–96.90	90.30–96.00	
MCH (pg)				
Mean (SD)	31.12 (1.93)	30.80 (2.20)	31.27 (1.77)	<0.0001
Median (min–max)	31.10 (19.8–42.4)	30.80 (19.8–40.7)	31.20 (22.9–42.4)	
1Q–3Q	30.00–32.30	29.50–32.10	30.20–32.40	

Table 1 continued

Variable	Total (n = 2,930)	Anemia[a] (n = 946)	Without anemia (n = 1,984)	P value
MCHC (g/dL)				
Mean (SD)	33.35 (1.07)	33.00 (1.15)	33.52 (0.98)	<0.0001
Median (min–max)	33.40 (28.8–37.0)	33.10 (28.8–36.7)	33.60 (29.6–37.0)	
1Q–3Q	32.70–34.10	32.20–33.80	32.80–34.20	
Serum albumin (g/dL)				
Mean (SD)	3.97 (0.43)	3.81 (0.46)	4.04 (0.40)	<0.0001
Median (min–max)	4.00 (1.4–5.3)	3.90 (1.6–4.9)	4.10 (1.4–5.3)	
1Q–3Q	3.70–4.20	3.60–4.10	3.80–4.30	
Ferritin (ng/dL)				
Mean (SD)	137.56 (137.45)	147.69 (158.37)	131.71 (123.47)	0.0280
Median (min–max)	100.00 (2.6–1,520.0)	107.00 (2.6–1,520.0)	98.00 (4.1–1,088.9)	
1Q–3Q	51.00–183.00	49.70–194.90	51.00–171.00	
TSAT (%)				
Mean (SD)	30.89 (12.25)	30.97 (13.38)	30.85 (11.61)	0.8814
Median (min–max)	29.73 (3.0–94.7)	29.93 (3.0–94.7)	29.63 (6.2–92.7)	
1Q–3Q	22.52–37.96	21.96–39.10	22.89–37.48	

ASO arteriosclerosis obliterans, *BMI* body mass index, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *TSAT* transferrin saturation, *1Q–3Q* first quartile to third quartile range

[a] Anemia is defined as an Hb level of <11 g/dL or receiving ESA therapy

[b] Average of three measurements

[c] Corrected with urinary creatinine

Table 2 Distribution of patients (n = 2,930)

ESA therapy	Iron therapy	No. of patients (%)	
		Hb < 11 g/dL	Hb ≥ 11 g/dL
Without	With	63 (2.2)	84 (2.9)
	Without	498 (17.0)	1,900 (64.8)
With	With	71 (2.4)	24 (0.8)
	Without	198 (6.8)	92 (3.1)

Anemia is defined as an Hb level of <11 g/dL or receiving ESA therapy

(P < 0.0001), with 9.7% at >45 mL/min/1.73 m^2, 17.0% between 30 and <45 mL/min/1.73 m^2, 40.5% between 15 and <30 mL/min/1.73 m^2 and 55.3% at <15 mL/min/1.73 m^2 (Table 4). The percentage of patients receiving iron therapy was 6.5, 13.7, 15.2 and 21.1%, respectively (P = 0.0365) (Table 5).

Table 6 shows ESA dosage and dosing frequencies. Information on dosage and dosing frequency is available for 273 of the 385 patients on ESA therapy and indicates that 1.1% were receiving ESA at least once a week, 30.4% once every 2 weeks, 67.8% once every 3 weeks or monthly, and 0.7% once every 2 months. Of the 273 patients, 83 (30.4%) were receiving ESA at the approved dosage and administration.

The mean Hb level was 10.28 ± 1.19 g/dL (mean ± SD) among the 385 patients on ESA therapy, with 116 (30.1%) of these patients showing an Hb level of ≥11 g/dL. Furthermore, in the group of 273 patients whose statistical data regarding dosing frequency are shown in Table 7, the percentage of those who achieved the target Hb level of ≥11 g/dL was 31.6% in the subgroup receiving ESA at a frequency of less than once every 2 weeks and was slightly lower than 39.5% in the subgroup receiving ESA above the approved dosage interval. The percentage of patients with ≥10 g/dL was 61.6% (237 of 385). In the group of 273 patients, the percentage of patients who achieved an Hb level of ≥10 g/dL was 67.4% in the subgroup of patients receiving ESA above the approved dosage interval and 64.7% in the subgroup receiving ESA at a frequency of less than once every 2 weeks (Table 7).

In contrast, the percentage of patients receiving no ESA therapy was 67.6 and 55.7%, respectively, among those with an Hb level of <11 and <10 g/dL.

Background factors that influence anemia or ESA therapy

Table 8 shows the background factors that affect anemia, with multivariate analyses showing factors of statistical

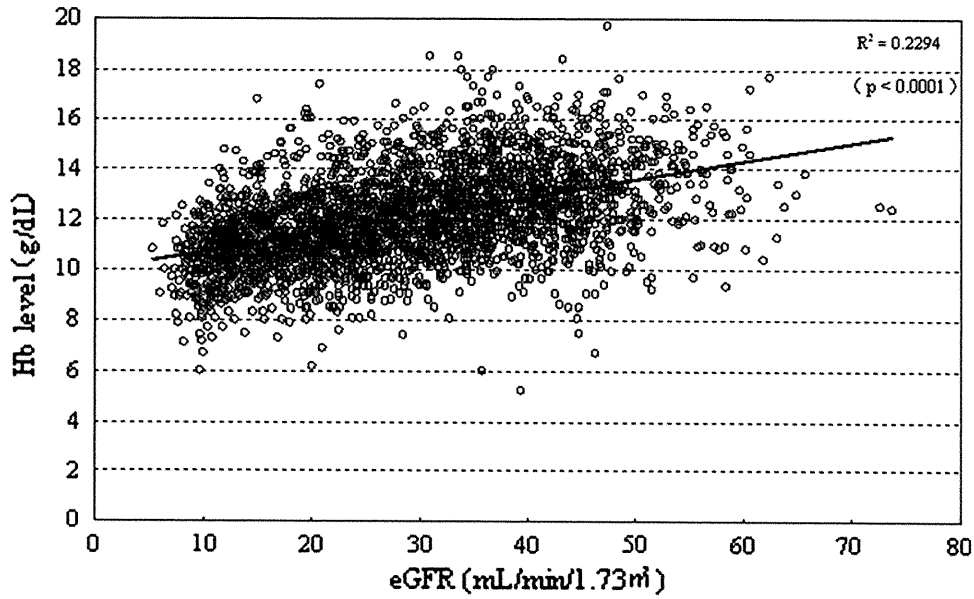

Fig. 1 Correlation between eGFR and Hb level

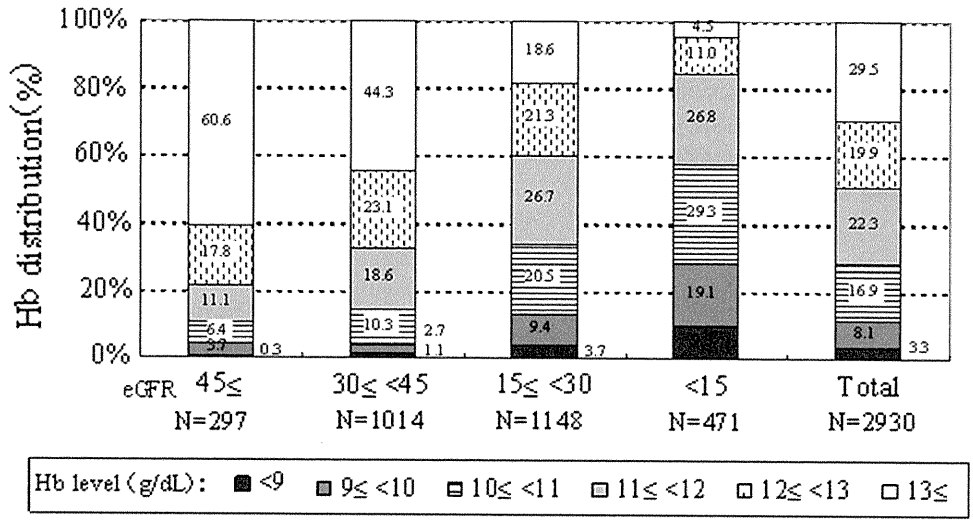

Fig. 2 Distribution of Hb level stratified by eGFR. The percentage of patients having an Hb level of <11 g/dL increased as eGFR declined

significance to be diabetic nephropathy, the main cause of CKD, and low levels of eGFR and serum albumin.

Table 9 shows the assessment results on patient characteristics that affect ESA therapy. Multivariate analyses showed, with statistical significance, that diabetic nephropathy, the main cause of CKD, and low levels of eGFR and serum albumin, were associated with lower odds of ESA therapy.

Discussion

Anemia is an independent risk factor for cardiovascular disease (CVD) [3, 4]. In CKD patients, kidney and cardiac diseases progress in a vicious circle (cardio-renal anemia syndrome) [3–5]. While many of the risk factors for CKD and CVD are difficult to intervene, it is possible to treat anemia by ESA and/or iron supplementation. Reports suggested that treating anemia may allow control of this vicious circle [5–7].

Meanwhile, large-scale intervention studies of CKD patients such as CHOIR [8] or CREATE [9] reported higher rates of composite CV endpoint or early initiation of renal replacement therapy for ESA therapy, with a target Hb of ≥13 g/dL compared with the slightly lower target Hb of 10.5–11.5 g/dL. Reports also indicated that in the TREAT study conducted in CKD patients with type 2 diabetes and an Hb level of <11 g/dL, the ESA therapy group that maintained Hb at 13 g/dL showed increased rates of stroke and cancer mortality among those with a history of cancer; however, there was no difference in all cause mortality or CVD incidence, when compared with the placebo group. In response to these reports, the US and European guidelines [10, 11] lowered their target Hb to between 11 and 12 g/dL for ESA therapy.

In 2008, the Japanese Society of Dialysis Therapy [12], and in 2009, the Japanese Society of Nephrology, established treatment guidelines for renal anemia in CKD patients to promote appropriate anemia management in CKD patients, setting a target Hb of ≥11 g/dL and an Hb level of >13 g/dL for dose reduction or withdrawal of ESA therapy (12 g/dL for patients with a CV complication or other medically required conditions). In the present study, we analyzed the data taken at survey initiation of the CKD-JAC study to examine factors associated with anemia management in Japanese CKD patients. The percentage of patients with anemia (defined as patients with an Hb of <11 g/dL or patients receiving ESA therapy) increased along with the progression of CKD stage, and multivariable analyses identified diabetic nephropathy as well as low serum albumin level as contributing factors to anemia, suggesting a need for early treatment of anemia in patients with diabetes or low serum albumin level. It appeared that a low serum albumin level was related to dietary therapy, dilution of blood due to fluid retention, or proteinuria.

Table 3 Distribution of anemia by eGFR (%)

eGFR	No. of patients (n = 2,930)	Patients with anemia (n = 946)
45≤	297	31 (10.4)
≥30 to <45	1,014	153 (15.1)
≥15 to <30	1,148	440 (38.3)
<15	471	322 (68.4)

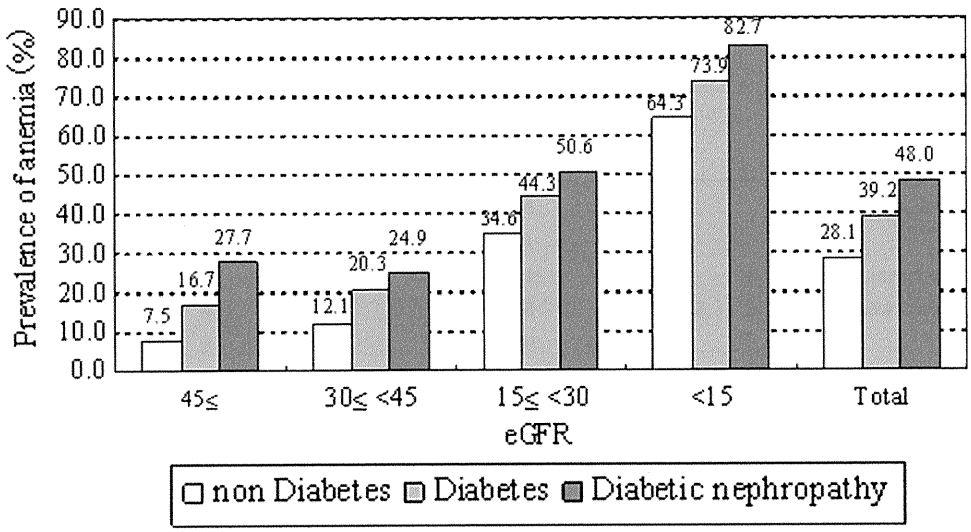

Fig. 3 Prevalence of patients with anemia by eGFR among diabetics and nondiabetics. The prevalence of anemia was higher in diabetic patients compared with nondiabetic patients

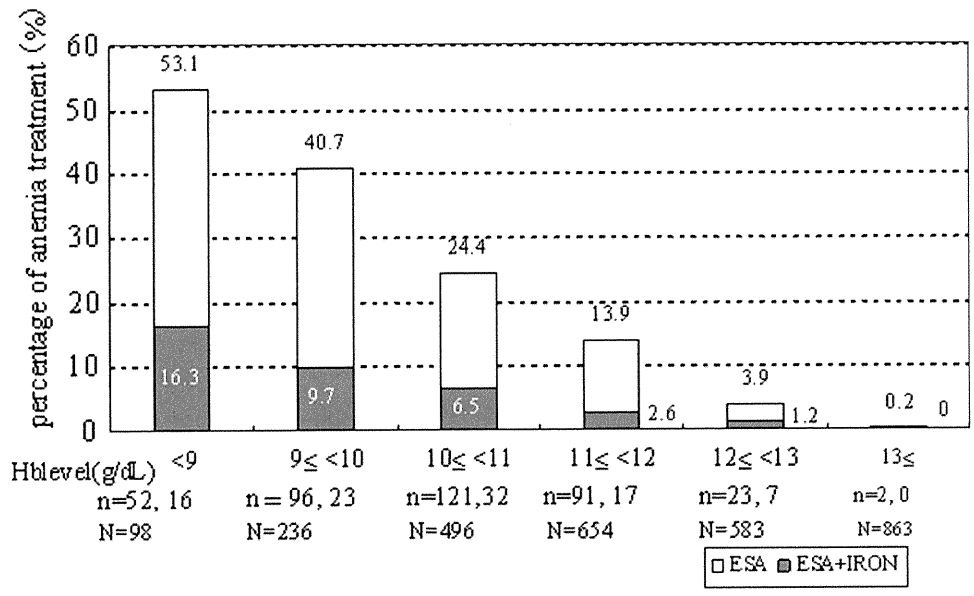

Fig. 4 Percentage of patients receiving anemia treatment by Hb level. The percentage of patients receiving anemia treatment increased as the Hb level declined

Table 4 Distribution of ESA therapy in anemia patients by eGFR (%)

eGFR	No. of patients with anemia (n = 946)	Hb < 11 g/dL not on ESA (n = 561)	Hb < 11 g/dL on ESA (n = 269)	Hb ≥ 11 g/dL on ESA (n = 116)	ESA therapy (n = 385)
45≤	31	28 (90.3)	3 (9.7)	0 (0.0)	3 (9.7)
≥30 to <45	153	127 (83.0)	15 (9.8)	11 (7.2)	26 (17.0)
≥15 to <30	440	262 (59.5)	123 (28.0)	55 (12.5)	178 (40.5)
<15	322	144 (44.7)	128 (39.8)	50 (15.5)	178 (55.3)

Table 5 Distribution of iron therapy in anemia patients by eGFR (%)

eGFR	No. of patients with anemia (n = 946)	Hb < 11 g/dL on iron (n = 63)	Hb < 11 g/dL on iron + ESA (n = 71)	Hb ≥ 11 g/dL on iron + ESA (n = 24)	Iron therapy (n = 158)
45≤	31	2 (6.5)	0 (0.0)	0 (0.0)	2 (6.5)
≥30 to <45	153	14 (9.2)	3 (2.0)	4 (2.6)	21 (13.7)
≥15 to <30	440	27 (6.1)	31 (7.0)	9 (2.0)	67 (15.2)
<15	322	20 (6.2)	37 (11.5)	11 (3.4)	68 (21.1)

Table 6 Distribution of ESA dosage and dosing frequencies

Dosing frequency	n (%)	Dosage		No. of patients achieving Hb level			
				Hb < 11	Hb ≥ 11	Hb < 10	Hb ≥ 10
>Once/week	2 (0.7)	6,000 U	1	0	1	0	1
		12,000 U	1	1	0	0	1
Once/week	1 (0.4)	12,000 U	1	0	1	0	1
Once/2 weeks[a]	83 (30.4)	6,000 U[a]	16	8	8	2	14
		9,000 U[a]	3	1	2	0	3
		12,000 U[a]	64	42	22	26	38
Once/3 weeks	13 (4.8)	6,000 U	3	1	2	0	3
		12,000 U	10	9	1	5	5
Once/month	172 (63.0)	3,000 U	2	0	2	0	2
		6,000 U	27	20	7	9	18
		9,000 U	1	0	1	0	1
		12,000 U	142	96	46	50	92
Once/2 months	2 (0.7)	12,000 U	2	2	0	2	0
Total	273	–	273	180	93	94	179

[a] The dosage and dosing frequency approved in Japan are: "The initial dose for subcutaneous injection should be 6,000 IU, which is administered once a week. When anemia-improving effects are achieved, the dose is administered at 6,000–12,000 IU once every 2 weeks"

Table 7 Distribution of ESA dosing frequencies by Hb level (%)

Dosing frequency	n (%)	Achievement of Hb level			
		Hb < 11 g/dL	Hb ≥ 11 g/dL	Hb < 10 g/dL	Hb ≥ 10 g/dL
≥Once/2 weeks[a]	86 (31.5)	52 (60.5)	34 (39.5)	28 (32.6)	58 (67.4)
<Once/2 weeks[b]	187 (68.5)	128 (68.4)	59 (31.6)	66 (35.3)	121 (64.7)
Total	273	180 (65.9)	93 (34.1)	94 (34.4)	179 (65.6)

[a] "≥Once/2 weeks" includes >once/week, once/week and once/2 weeks

[b] "<Once/2 weeks" includes once/3 weeks, once/month and once/2 months

Table 8 Factors associated with anemia (univariate and multivariate logistic regression analysis)

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Sex (female)	2.096 (1.789–2.456)	<0.0001		
Age (≥65 year)	1.766 (1.511–2.065)	<0.0001		
Causative diseases of CKD				
Diabetic nephropathy	2.357 (1.963–2.830)	<0.0001	1.899 (1.530–2.357)	<0.0001
Glomerulonephritis	0.685 (0.582–0.806)	<0.0001		
Others	0.773 (0.659–0.906)	0.0015		
Medical history				
Hypertension	1.294 (1.053–1.591)	0.0145	0.952 (0.750–1.208)	0.6857
Myocardial infarction	0.995 (0.697–1.421)	0.9799		
Angina	1.260 (0.963–1.649)	0.0919		
Congestive heart failure	1.553 (1.062–2.272)	0.0231	1.016 (0.649–1.590)	0.9463
ASO	1.744 (1.182–2.574)	0.0051		
Stroke	1.148 (0.905–1.456)	0.2554		
Diabetes	1.655 (1.413–1.938)	<0.0001		
Cancer	0.894 (0.660–1.211)	0.468		
Serum creatinine (mg/dL)	2.168 (1.993–2.357)	<0.0001		
eGFR (mL/min/1.73 m^2)	0.914 (0.906–0.922)	<0.0001	0.916 (0.908–0.924)	<0.0001
P (mg/dL)	3.138 (2.719–3.623)	<0.0001		
CRP (≥1 mg/dL)	1.806 (1.229–2.656)	0.0026		
Serum albumin (g/dL)	0.284 (0.233–0.346)	<0.0001	0.355 (0.285–0.441)	<0.0001

OR odd ratio, *CI* confidence interval

Table 9 Factors associated with ESA therapy (univariate and multivariate logistic regression analysis)

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Sex (female)	1.637 (1.319–2.031)	<0.0001		
Age (≥65 year)	1.848 (1.487–2.298)	<0.0001		
Causative diseases of CKD				
Diabetic nephropathy	2.236 (1.771–2.823)	<0.0001	1.641 (1.248–2.157)	0.0004
Glomerulonephritis	0.603 (0.477–0.763)	<0.0001		
Others	0.847 (0.679–1.056)	0.1398		
Medical history				
Hypertension	1.925 (1.381–2.683)	0.0001	1.367 (0.949–1.969)	0.0932
Myocardial infarction	0.865 (0.516–1.452)	0.5834		
Angina	1.118 (0.772–1.619)	0.5555		
Congestive heart failure	1.521 (0.935–2.473)	0.0908	0.962 (0.553–1.671)	0.8897
ASO	1.451 (0.873–2.410)	0.1511		
Stroke	1.289 (0.943–1.762)	0.1120		
Diabetes	1.766 (1.424–2.191)	<0.0001		
Cancer	1.091 (0.730–1.630)	0.6718		
Serum creatinine (mg/dL)	2.192 (1.997–2.407)	<0.0001		
eGFR (mL/min/1.73 m^2)	0.884 (0.871–0.897)	<0.0001	0.885 (0.872–0.899)	<0.0001
P (mg/dL)	2.973 (2.512–3.518)	<0.0001		
CRP (≥1 mg/dL)	1.525 (0.941–2.470)	0.0868		
Serum albumin (g/dL)	0.379 (0.301–0.478)	<0.0001	0.514 (0.392–0.675)	<0.0001

OR odd ratio, *CI* confidence interval

The percentage of CKD patients receiving anemia treatment increased as the Hb level declined, but patients on ESA therapy accounted for only 32.4% of those with an Hb of <11 g/dL. Even among patients with an Hb of <10 g/dL, the ESA use was only 44.3%. These results suggest that not enough anemic patients are receiving ESA therapy. The rates of ESA use by CKD progression showed that the earlier the CKD stage, the less ESA therapy was prescribed to treat anemia. Even when the Hb level dropped to below 11 g/dL, the rate of patients not on ESA therapy remained high, suggesting a low awareness for anemia treatment in the early stages. Multivariate analyses of patient characteristics that influence ESA therapy also identified low eGFR levels, reflecting the difficulty of administering ESA at high eGFR levels, or, in other words, in the early stages of CKD.

Analyses of dosing frequency of ESA revealed that only 30.4% of patients were receiving ESA at the approved dosage and administration and that most patients (67.8%) were receiving ESA once every 3 weeks or monthly, indicating that the current practice of anemia treatment for CKD patients deviates from the approved dosage interval for the current ESA preparations.

The mean Hb level was 10.28 ± 1.19 g/dL (mean ± SD) among all patients undergoing ESA therapy. Patients who had an Hb level of ≥11 g/dL, the target level proposed by the treatment guideline for renal anemia in CKD patients [12], accounted for 30.1%. Among these patients, 39.5% were receiving ESA based on the currently approved dosage interval or more frequently, and 31.6% were on lower dosing frequencies, showing a low percentage of patients were achieving the target Hb level proposed by the treatment guideline through ESA therapy, with such a trend being more prominent among patients receiving less frequent treatment of ESA. This can be attributed to the difficulty for outpatients with early stage CKD to visit a hospital for the sole purpose of receiving ESA with few subjective symptoms.

At the start of the present study in 2007, with no treatment guidelines available in Japan for renal anemia in CKD patients not on dialysis, anemia treatment was based on an approximate level of 10 g/dL, which is the target Hb level provided in the current ESA package insert. The results from the present study showed that even when adhering to this level, the present ESA does not provide adequate anemia management in CKD patients. We expect the CKD-JAC study to show how such inadequate anemia management affects the outcome of CKD patients.

Acknowledgments This study was conducted by principal investigators at the following medical centers: Sendai Social Insurance Hospital (Miyagi), Toride Kyodo Hospital (Ibaraki), Jichi Medical University (Tochigi), Tokyo Women's Medical University Hospital (Tokyo), St. Luke's International Hospital (Tokyo), Showa University Hospital (Tokyo), Showa University Yokohama Northern Hospital (Kanagawa), Showa University Fujigaoka Hospital (Kanagawa), Gifu Prefectural General Medical Center (Gifu), Kasugai Municipal Hospital (Aichi), Tosei General Hospital (Aichi), Osaka University Hospital (Osaka), Osaka General Medical Center (Osaka), Osaka City General Hospital (Osaka), Kurashiki Central Hospital (Okayama), Fukuoka Red Cross Hospital (Fukuoka), Iizuka Hospital (Fukuoka).

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