研究成果の刊行に関する一覧表

雑誌

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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ORIGINAL ARTICLE

Patterns in the prevalence of hepatitis C virus infection at the start of hemodialysis in Japan

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Abstract
Background Although hepatitis C virus (HCV) infection is a persistent public health concern in hemodialysis patients, there seem to have been only a few reports on the prevalence of HCV at the start of hemodialysis. In this study we investigated whether patients starting on hemodialysis therapy are positive for anti-HCV antibody or not.
Methods The 400 patients who began regular hemodialysis between February 2003 and June 2007 were enrolled in this study. Clinical data such as age, anti-HCV antibody and primary cause of end-stage kidney disease (ESKD) were examined. As healthy controls we used 70,717 healthy blood donors in 2005 whose data were obtained from Tokyo Metropolitan Red Cross Blood Center. Anti-HCV antibody was used as an indicator of HCV infection. Since the prevalence of HCV infection is affected by age in Japan, we classified the patients by age group.
Results The anti-HCV antibody prevalence rate among the patients who were new to hemodialysis was 7.3%, as opposed to 0.15% in the healthy volunteers. The prevalence of HCV in the 31–45-, 46–60-, and 61-year-old groups was significantly higher among the hemodialysis patients than among the healthy volunteers ($P = 0.0209$, <0.0001, and <0.0001, respectively). The prevalence rate of anti-HCV antibody was higher among men (10.0%) than among women (1.5%, $P < 0.0001$) in the hemodialysis patients. The anti-HCV-antibody-positive patients were significantly older than the anti-HCV-antibody-negative patients (66.4 ± 14.3 years versus 58.6 ± 16.6 years; $P = 0.0152$). Diabetic nephropathy was a more frequent cause of ESKD among the anti-HCV-antibody-positive patients (30.4%) than among the anti-HCV-antibody-negative patients (19.9%, $P = 0.0122$). Among the anti-HCV-antibody-positive patients, 55.2% had received a blood transfusion. The rate was significantly higher than that among the anti-HCV-antibody-negative patients (19.4%, $P < 0.0001$).
Conclusion The results showed a much higher rate of anti-HCV antibody positivity in patients new to hemodialysis than in healthy volunteers. Older age, blood transfusion, male gender, and diabetic nephropathy seemed to be risk factors for anti-HCV antibody positivity in Japan.

Keywords Hepatitis C · Hemodialysis · Diabetic nephropathy · Diabetes mellitus · End-stage kidney disease (ESKD) · Liver chirrhosis

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Introduction

Hepatitis C virus (HCV) infection is a persistent public health concern in hemodialysis patients. Unlike hepatitis B virus (HBV), no vaccine is available for HCV [1]. Patients infected with HCV often have minimal clinical evidence of disease [1, 2], but HCV infection has been associated with greater morbidity and mortality in ESKD patients [2–4].

The number of patients on hemodialysis infected with HCV is rather high [5], mostly as a result of nosocomial infection. Recent dialysis outcomes and practice patterns study (DOPPS) have revealed a mean facility prevalence in France, Germany, Italy, Japan, Spain, the UK, and the US of 13.5% and the mean prevalence according to country ranged from 2.6 to 22.9% [6]. The main causes of nosocomial infection by HCV in hemodialysis patients are filter reuse, use of contamined hemodialysis machines, and contamination of medical staff's hands [7].

Nevertheless, there seem to have been only a few reports on the prevalence of HCV at the start of hemodialysis. Some ESKD patients may be at risk of exposure to HCV associated with medical treatment, including blood transfusion, and ESKD patients are thought to be susceptible to HCV infection because of the decline in immune response. Hepatitis C is both a cause and a complication of chronic kidney disease. Chronic infection with HCV can lead to the immune complex syndromes of cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN). Management of HCV-related cryoglobulinemia and MPGN is difficult: antiviral therapy is effective in clearing HCV infection in a proportion of patients, but these conditions can be severe and resistant to antiviral therapy [8]. Glomerular abnormalities in liver cirrhosis patients are also known, even though their renal insufficiency is generally mild.

An overview of regular dialysis treatment in Japan revealed that the proportion of patients who had been on hemodialysis therapy for less than 2 years who were positive for anti-HCV antibody was 7.6% [9], a higher rate than in the general population in Japan.

We therefore hypothesized that HCV infection is already relatively widespread at the start of hemodialysis therapy, and in the present study, we investigated whether patients who start hemodialysis therapy are already anti-HCV-antibody-positive.

Materials and methods

The 400 patients who started on regular hemodialysis in our kidney center at Tokyo Women's Medical University Hospital between February 2003 and June 2007 were enrolled in this study.

Age, gender, HBs antigen (Ag), HBs antibody (Ab), treponema pallidum latex immuno assay (TPLA), and primary cause of ESKD were examined. The proportions of patients starting on hemodialysis after having been on continous ambulatory peritoneal dialysis (CAPD) or having received a renal transplant were also examined. The blood chemistry, peripheral blood count and whether they had signs of liver fibrosis or hepatocellular carcinoma on abdominal echo examinations or had ever received a blood transfusion were examined.

Table 1 Prevalence of HCV in patients new to hemodialysis therapy

	Ant-HCV Ab positive	Ant-HCV Ab negative	*P* value
Number	29	371	–
Age[a] (years)	66.4 ± 14.3	58.6 ± 16.6	0.0152
Gender (M/F)	27/2	242/129	<0.0001
CAPD[b] (%)	0	3.2	n.s.
Transplantation[b] (%)	10.3	7.8	n.s.
Positive for HBs Ag (%)	0	1.08	n.s.
Positive for HBs Ab (%)	34.8	19.1	n.s.
Positive for TPLA (%)	7.1	1.64	n.s.

CAPD continuous ambulatory peritoneal dialysis, *Ag* antigen, *Ab* antibody

TPLA treponema pallidum latex immuno assay mean ± SD

[a] Age at the start of hemodialysis therapy

[b] Rate of patients switching to hemodialysis from CAPD or transplantation

As healthy controls for the prevalence of HCV we used 70,717 healthy first-time blood donors in 2005 whose data were obtained from Tokyo Metropolitan Red Cross Blood Center [10]. Since the prevalence of HCV infection is affected by age, we classified the patients into the following age groups (years): under 31, 31–45, 46–60, and 61–70.

Data are reported as means ± SD. The chi-square (χ^2) test was used for comparisons between categorical variables. Fisher's exact test was used when the criteria for the χ^2 test could not be applied. Student's *t*-test was used for comparisons between continuous variables. All statistical calculations were performed with Stat View J 5.0 software. A *P* value of less than 0.05 was considered statistically significant.

Results

The overall anti-HCV antibody prevalence rate among patients new to hemodialysis was 7.3%. Table 1 compares the anti-HCV-antibody-positive and anti-HCV-antibody-negative patients. The anti-HCV-antibody-positive patients were significantly older than the anti-HCV-antibody-negative patients (66.4 ± 14.3 years versus 58.6 ± 16.6 years; $P = 0.0152$). The prevalence rate of anti-HCV antibody was higher among men (10.0%) than among women (1.5%, $P < 0.0001$) in the hemodialysis patients. The proportions of patients starting on hemodialysis after having been on CAPD or having received a transplant were similar in both patients, and the prevalence of HBs Ag or HBs Ab was also similar in both patients. The proportion

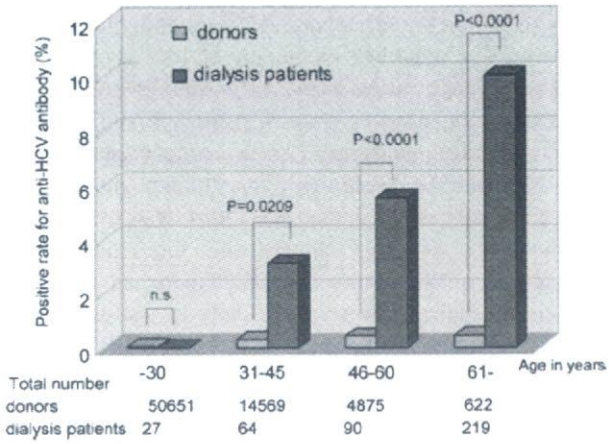

Fig. 1 Comparison between the prevalence of HCV in blood donors in Tokyo in 2005 and a new hemodialysis population in whole gender. Data on the prevalence in blood donors in Tokyo were obtained from the Tokyo Metropolitan Red Cross Blood Center

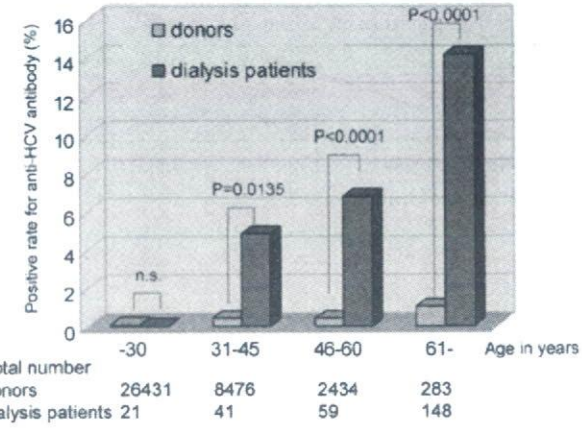

Fig. 2 Comparison between the prevalence of HCV in blood donors in Tokyo in 2005 and a new hemodialysis population in men. Data on the prevalence in blood donors in Tokyo were obtained from the Tokyo Metropolitan Red Cross Blood Center

positive for TPLA tended to be higher in anti-HCV-antibody-positive patients than in the anti-HCV-antibody-negative patients, but the difference was not statistically significant.

The anti-HCV antibody prevalence rate among the 70,717 blood donors in Tokyo in 2005 was 0.15%. Figure 1 compares the prevalence of HCV in the blood donors and the patients new to hemodialysis therapy. None of the patients new to hemodialysis in the under 31-year-old group were positive for anti-HCV antibody, whereas in the 31–45-, 46–60-, and 61-year-old groups the prevalence of HCV was significantly higher in the hemodialysis patients than in the healthy volunteers ($P = 0.0209$, <0.0001, <0.0001, respectively).

Among the 37,624 healthy male volunteers, 72 (0.19%) were positive for anti-HCV antibody, while among the 33,093 healthy female volunteers, 36 (0.11%) were positive. Similar to the trend among hemodialysis patients, the prevalence rate of anti-HCV antibody was also significantly higher among healthy male volunteers than among healthy female volunteers ($P = 0.005$). As only two women were positive for anti-HCV antibody among the hemodialysis patients, we could not compare the difference in HCV prevalence between female hemodialysis patients and female healthy volunteers. Figure 2 compares the prevalence of HCV among the blood donors and patients new to hemodialysis therapy among men. The result was similar to the overall trend for both genders.

Table 2 shows the primary causes of ESKD. Diabetic nephropathy was a more frequent cause of ESKD in the anti-HCV-antibody-positive patients (37.9%) than in the anti-HCV-antibody-negative patients (18.6%, $P = 0.0122$).

Table 3 shows the blood chemistry results, peripheral blood count, results of abdominal echography, and the history of blood transfusion for the anti-HCV-antibody-positive and anti-HCV-antibody-negative patients new to hemodialysis therapy. The total bilirubin and asparate aminotransferase levels were statistically higher among anti-HCV-antibody-positive patients (0.4 ± 0.4 mg/dl and 28.9 ± 23.3 IU/l, respectively) than among anti-HCV-antibody-negative patients (0.3 ± 0.2 mg/dl; $P = 0.0012$,

Table 2 Primary cause of end-stage kidney disease

Cause of ESKD (%)	Ant-HCV antibody positive	Ant-HCV antibody negative	*P* value
Chronic glomerulonephritis	6 (20.7%)	150 (40.4%)	n.s.
Chronic pyelonephritis	0 (0%)	1 (0.3%)	n.s.
RPGN	1 (3.4%)	9 (2.4%)	n.s.
Nephropathy of toxemia of pregnancy	0 (0%)	3 (0.8%)	n.s.
Other unclassified nephritis	1 (3.4%)	6 (1.6%)	n.s.
Polycystic kidney disease	1 (3.4%)	14 (3.8%)	n.s.
Nephrosclerosis	1 (3.4%)	51 (13.7%)	n.s.
Diabetic nephropathy	11	(37.9%)	69
(18.6%)	0.0122		
Lupus nephritis	2 (6.9%)	4 (1.1%)	n.s.
Urate nephropathy	0 (0%)	2 (0.5%)	n.s.
Urolithiasis	0 (0%)	3 (0.8%)	n.s.
Tumor of kidney or urinary tract	1 (3.4%)	3 (0.8%)	n.s.
Obstructive uropathy	0 (0%)	1 (0.3%)	n.s.
Myeloma kidney	0 (0%)	2 (0.5%)	n.s.
Renal dysplasia	0 (0%)	2 (0.5%)	n.s.
Unknown	0 (0%)	8 (2.2%)	n.s.
After renal transplantation	3 (10.3%)	29 (7.8%)	n.s.
Others	2 (6.9%)	14 (3.8%)	n.s.

RPGN rapidly progressive glomerulonephritis

Table 3 Characteristics of patients new to hemodialysis therapy

Category	Ant-HCV antibody positive	Ant-HCV antibody negative	*P* value
Total bilirubin (mg/dl)	0.4 ± 0.4	0.3 ± 0.2	0.0012
Asparate aminotransferase (IU/l)	28.9 ± 23.2	18.6 ± 16.7	0.0022
Alanine aminotransferase (IU/l)	25.2 ± 17.4	17.3 ± 25.5	n.s.
Fe (μg/dl)	58.4 ± 60.8	59.4 ± 35.3	n.s.
Total iron binding capacity (μg/dl)	222 ± 58	227 ± 51	n.s.
Ferritin (ng/ml)	354 ± 273	305 ± 472	n.s.
White blood cell count (/μl)	6,400 ± 3,240	6,750 ± 2,720	n.s.
Red blood cell count ($\times 10^6$/μl)	2.78 ± 0.58	2.85 ± 0.54	n.s.
Hemoglobin (g/dl)	8.4 ± 1.4	8.6 ± 1.6	n.s.
Hematocrit (%)	25.5 ± 4.6	26.2 ± 4.9	n.s.
Platelet count ($\times 10^4$/μl)	17.0 ± 7.1	19.8 ± 8.2	n.s.
Liver fibrosis (%)	25.0	4.9	0.0002
Hepatocellular carcinoma (%)	17.9	1.4	<0.0001
Blood transfusion (%)	55.2	19.4	<0.0001

Mean ± SD

18.6 ± 16.7 IU/l; $P = 0.0022$). The alanine aminotransferase level tended to be higher among the anti-HCV-antibody-positive patients (25.2 ± 17.4 IU/l) than among the anti-HCV-antibody-negative patients (17.3 ± 25.5 IU/l). Iron-related markers like the Fe level, the total iron-binding capacity, and the ferritin level were almost the same among anti-HCV-antibody-positive and anti-HCV-antibody-negative patients. Similarly, the white blood cell count, hemoglobin and hematocrit levels were almost the same, but the platelet count tended to be lower among the ant-HCV-antibody-positive patients ($17.0 \pm 7.1 \times 10^4$/μl) than among the anti-HCV-antibody-negative patients ($19.8 \pm 8.2 \times 10^4$/μl). The rates of liver fibrosis and hepatocellular carcinoma were statistically higher among anti-HCV-antibody-positive patients (25.0% and 17.9%) than among anti-HCV-antibody-negative patients (4.9%; $P = 0.0002$, 1.4%; $P < 0.0001$). Among the anti-HCV-antibody-positive patients, 55.2% had received a blood transfusion. This rate was significantly higher than that among the anti-HCV-antibody-negative patients (19.4%, $P < 0.0001$).

Discussion

The prevalence of HCV infection at the start of hemodialysis therapy has never been clearly described in Japan. A study in Italy reported an anti-HCV-antibody-positive rate at the start of hemodialysis therapy of 13% [11]. An anti-HCV prevalence rate of 14.4% at the start of hemodialysis therapy was reported by a study in the US, and age, race, gender, and drug abuse were all independent predictors of anti-HCV antibody positivity in that study population [12]. The US study reported that age (50>) was a significant predictor, that younger patients were more likely to be infected with HCV, and that black men and former or current drug abusers were more likely to test positive for anti-HCV antibody. Presumably, such high-risk behaviors as drug abuse are more common among younger patients, men, and blacks, thereby contributing to the high frequency of HCV infection in incident dialysis patients belonging to these patient groups [12]. The prevalence of anti-HCV antibody among patients new to hemodialysis in our study was 7.3%. As Fig. 1 shows, the prevalence of anti-HCV antibody was significantly higher among patients new to hemodialysis than among the healthy controls in subjects over the age of 31 years. Similar to the results of a study conducted in the US, male gender was a risk factor for anti-HCV-antibody positivity in this study. On the other hand, the anti-HCV-antibody-positive patients were older than the anti-HCV-antibody-negative patients at the start of hemodialysis, and the rate of patients who had received a blood transfusion was higher among the anti-HCV-antibody-positive patients than among the anti-HCV-antibody-negative patients. In contrast to the US, older age and blood transfusion may be risk factors in Japanese patients. Donor blood was not routinely screened for HCV infection in Japan until 1989. Older patients may have received unscreened blood that transmitted HCV infections.

HCV infection may cause ESKD, but none of the patients had ever undergone a renal biopsy and been diagnosed with HCV-related glomerulonephritis. The frequent presence of glomerular abnormalities in patients with liver cirrhosis was first noted during the 1940s. The renal insufficiency is generally mild in such patients. Twenty-five percent of patients positive for anti-HCV antibody already had liver fibrosis. The total bilirubin and asparate aminotransferase levels were statistically higher among the anti-HCV-antibody-positive patients than among the anti-HCV-antibody-negative patients. The alanine aminotransferase level tended to be higher, and platelet count tended to be lower among the anti-HCV-antibody-positive patients than among the anti-HCV-antibody-negative patients. Renal dysfunction secondary to liver fibrosis may have affected their renal survival even though the primary cause of the ESKD was something else, for example diabetic nephropathy.

Our hospital has two hemodialysis rooms, one in the kidney center and the other in the diabetes center. The subjects of this study were patients who started

hemodialysis in the kidney center, so the percentage of patients who started on hemodialysis for ESKD secondary to diabetic nephropathy was relatively low.

A high prevalence of HCV has been reported in patients with type-two diabetes mellitus (DM) [13]. The high prevalence may be related to increased vulnerability to HCV infection because of impaired immune defence mechanisms in DM. Also, some patients with various forms of liver disease are predisposed to impaired glucose tolerance because of corticosteroid and hydrochlorothiazide therapy or the presence of hemochromatosis [14]. In addition to these known risk factors, there are emerging epidemiological data suggesting that HCV infection may also contribute to the development of diabetes [15]. Two reports have mentioned the high prevalence of HCV infection among hemodialysis patients with diabetes mellitus [13, 16]. Our study revealed that diabetic nephropathy was a more frequent cause of ESKD among Japanese patients who were anti-HCV-antibody positive at the start of hemodialysis (37.9%) than among those who were anti-HCV-antibody negative (18.6%, $P = 0.0122$).

The prevalence of HCV was not very high among the patients starting on hemodialysis after having been on CAPD or who had received a transplant. Previous CAPD or transplantation was not a risk factor for HCV infection in this study.

Low levels of iron and ferritin are advantageous for the activity of hepatitis because of the reduced reactive oxidative stress. However, no differences in the iron and ferritin levels were observed between the anti-HCV-antibody-positive and the anti-antibody-negative patients.

One of the limitations of this study is that Tokyo Metropolitan Red Cross Blood Center accepts volunteers who do not have history of blood transfusion, history of viral hepatitis, or other risk factors as blood donors. So the volunteer blood donors, even first time ones, have been documented to have lower infection rates than the general population.

An overview of regular dialysis treatment in Japan reported a 7.6% anti-HCV antibody-positive rate among patients who had been on hemodialysis therapy for less than 2 years [9], and there were no statistical differences between the patients with less than 2 years hemodialysis in their study and the patients new to hemodialysis in our study. Acquisition of hepatitis C from nosocomial sources after starting on dialysis therapy appears to be much less of a factor now.

Conclusion

The results of this study showed a much higher rate of anti-HCV antibody positivity in patients new to hemodialysis than in healthy volunteers. Older age, blood transfusion, male gender, and diabetic nephropathy seemed to be risk factors for anti-HCV antibody positivity in Japan.

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原　著

当院における原因不明の発熱で入院した慢性腎臓病患者の特徴

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key words：不明熱，感染症，膠原病，結核，アミロイドーシス

〈要旨〉
目的：血液透析患者の発熱は腎不全に伴う内部環境変化と透析療法に伴う合併症の影響により，特有な病態を呈しており，しばしば原因の同定に苦慮する場合がある．慢性腎臓病患者において透析の有無や透析歴で原因不明の発熱の原因を検討した報告は少なく，今回，慢性腎臓病患者において，血液透析の有無によって発熱の原因に違いがないか，血液透析患者の発熱に対し留意する点がないかを検討した．方法・対象：当院に原因不明の37℃以上の発熱で1998年8月から2007年7月まで入院した100例を対象とした．入院精査によって得た診断名をchronic kidney disease（CKD）stage分類に基づき分類し発熱の原因を比較した．また，血液透析患者に関しては発熱の原因と透析歴の関連について検討した．結果：CKD stage 5Dの患者42例は全例血液透析患者であった．発熱の原因としては，29例が感染症で，6例が透析アミロイドーシス，2例が悪性腫瘍，1例が薬剤性，4例が不明のままであった．一方，CKD stage 1～5の患者58例のうち39例が感染症，9例が膠原病，3例が悪性腫瘍，1例が薬剤性で6例が不明のままであった．発熱の原因として膠原病は血液透析患者ではそのほかのCKD stageの患者に比較し有意に低率であった（0% vs. 18.4%，p＝0.0094）．透析アミロイドーシスと診断した症例の透析歴は平均23.1±5.0年（16～29年）であり，ほかの原因による発熱に比較し透析歴が長期であった（p＜0.0001）．感染症のうち，塗抹，培養，核酸増幅法によって結核と診断した症例が血液透析患者に2例認めたのに対し，ほかのCKD stageの患者では認めなかった．結語：血液透析患者において原因不明の発熱を認めた際，まず頻度が多く，治療が遅れた場合，致命的となりうることから感染症を疑うべきである．さらに結核の可能性，また透析歴の長い場合は透析アミロイドーシスに注意が必要である．

Characteristics of chronic kidney disease patients admitted to our hospital to investigate the cause of fever

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Objective：The cause of fever in hemodialysis patients is sometimes difficult to diagnose. We investigated whether there were differences between the causes of fever in hemodialysis patients and non-hemodialysis chronic kidney disease (CKD) patients, which was not diagnosed in outpatient examinations or at another hospital. Materials and Methods：We conducted a retrospective chart review of 100 CKD patients who were admitted to our hospital to investigate the cause of fever between August 1998 and April 2007. We classified the patients

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according to CKD stage and compared the causes of their fever as determined by a thorough examination. Results : The cause of the fever was infection in 29 of the 42 hemodialysis patients, malignancy in 2, hemodialysis-related amyloidosis in 6, and drug-associated in 1, and the cause remained unknown in 4. None of their fevers was caused by collagen disease. On the other hand, the cause of the fever was infection in 39 of the 58 stage 1 to 5 patients, collagen disease in 9, malignancy in 3, and drug-associated in 1, and it remained unknown in 6. Collagen disease was a less common cause of fever in hemodialysis patients than in the stage 1 to 5 patients (0% versus 18.4%, p=0.0094). The duration of hemodialysis in patients with hemodialysis-related amyloidosis was 23.1±5.0 (16−29) years. Of the 29 patients in whom the cause of fever was infection, 2 were shown to have tuberculosis based in the results of Gaffky and/or culture and/or the polymerase chain reaction, but none of the other stage patients was found to have tuberculosis. Conclusion : Infection should be considered when investigating the cause of fever in hemodialysis patients, because it is the most frequent cause and because delayed treatment is associated with increased mortality. Tuberculosis and amyloidosis should also be considered.

緒　言

血液透析患者の発熱は，腎機能低下に伴う内部環境変化，透析医療の合併症などにより特有の病態を呈している．そのため，発熱の原因疾患を同定することが困難である場合がある．原因不明熱と診断され，適切な治療が行えないこともしばしば経験される．慢性腎臓病患者において透析の有無や透析歴で原因不明の発熱の原因を検討した報告は少ない．そこでわれわれは，慢性腎臓病患者において，血液透析患者とchronic kidney disease（CKD）stage 1～5の患者において，原因疾患に偏りがないか，また，血液透析患者に関しては発熱の原因と透析歴の関連について検討した．

Ⅰ．対象と方法

1998年8月から2007年7月まで37℃以上の発熱をきたし，外来もしくは他院入院中で発熱の原因が不明で当科に入院した100症例を対象とした．

不明熱とは38.3℃以上の発熱が数回出現し，発熱が3週間以上継続し，3回以上の外来または3日以上の入院による適切な診断でも原因不明なものと定義されている[1]．実際の臨床では38℃以下の発熱でも治療の必要な疾患があり，比較的低温の発熱であっても早期に原因の検索を行うべきである．そこで，今回われわれは対象として定義上の不明熱の症例ではなく，37℃以上の発熱の症例で外来，他院で発熱の原因が不明で当院に入院した患者について検討した．

入院時の体温，CRP，白血球分画と精査の結果，至った診断名を検索した．血液透析患者は透析歴も検索した．MDRD式で推定糸球体濾過量を求め，CKD分類に基づき，発熱の原因を分類し，血液透析患者とそのほかで比較した．

三群間の平均の比較はANOVA，二群間はt検定を使用し，定性的変数間の比較はカイ二乗検定を使用して行った．カイ二乗検定が適切でない場合はFisherを使用した．統計はstat view SEを使用し，p=0.05以下を有意とした．

Ⅱ．結　果

1．腎機能別の患者背景

表1に腎機能別の患者背景を示した．CKD stage 5Dの患者は42例，全て血液透析患者で男性は20例，女性は22例であった．CKD stage 3～5の症例は41例で男性15例，女性26例であった．CKD stage 1～2の症例は17例，男性6例，女性11例であった．年齢は血液透析患者，CKD stage 3～5の症例はCKD stage 1～2の症例に比較し，高齢であった(p=0.003)．入院時の体温に3群で有意な差は認めなかった．CRPは血液透析症例において高値であった（p=0.049）のに対し，白血球数，好中球数に3群に有意差は認めず，リンパ球は血液透析症例において低値であった（p=0.010）．また，表2に腎症障害の原因の内訳を示した．透析患者において糖尿病性腎症が多い傾向にあった．SLE腎炎が透析患者で少なく（p=0.023），CKD stage 3～5の症例では多かった（p=0.047）．

2．腎機能別の発熱の原因疾患分類

表3に腎機能別の発熱の原因疾患分類を示した．それぞれの群で発熱の原因としては感染症が最も多く，それぞれ血液透析で29例（69.0%），CKD stage 3～5で28例（68.3%），CKD stage 1～2で11例（64.7%）であった．

血液透析患者の感染症の原因としては細菌性が，抗

表 1　腎機能別の患者背景

Stage	血液透析	3～5	1～2	p value
症例数	42	41	17	
性別（男/女）	20/22	15/26	6/11	
年齢	57.2±15.6	57.7±20.1	40.5±17.8	0.003
体温	38.0±0.8	38.3±1.0	38.2±0.9	n. s.
CRP（mg/dL）	12.8±10.1	9.5±9.4	6.5±5.7	0.049
白血球数（/μL）	9,500±6,380	10,100±6,200	9,890±5,400	n. s.
好中球（/μL）	7,460±6,050	8,000±5,190	7,070±3,790	n. s.
リンパ球（/μL）	1,080±650	1,160±1,150	2,030±1,720	0.010

（±：SD）

表 2　腎機能別の原疾患

Stage	血液透析	3～5	1～2
慢性糸球体腎炎（%）	20（40.7）	11（26.8）	7（41.2）
慢性腎盂腎炎（%）	0（0）	0（0）	2（11.8）
急速進行性糸球体腎炎（%）	1（2.4）	3（7.3）	0（0）
その他分類不能の腎炎（%）	0（0）	2（4.9）	1（5.9）
多発性嚢胞腎（%）	2（4.8）	2（4.9）	1（5.9）
腎硬化症（%）	3（7.1）	7（17.1）	2（11.8）
悪性高血圧症（%）	1（2.4）	0（0）	0（0）
糖尿病性腎症（%）	6（14.3）	1（2.4）	1（5.9）
SLE 腎炎（%）	1（2.4）*	8（19.5）**	2（11.8）
アミロイド腎（%）	0（0）	0（0）	1（5.9）
通風腎（%）	1（2.4）	0（0）	0（0）
骨髄腫（%）	0（0）	1（2.4）	0（0）
その他（%）	2（4.8）	1（2.4）	0（0）
不明（%）	5（11.9）	5（12.2）	0（0）

*：血液透析 vs. その他 p＝0.023
**：CKD stage 3～5 vs. その他 p＝0.047

表 3　腎機能別の発熱の原因疾患分類

Stage	血液透析	3～5	1～2
感染症（%）	29（69.0）#	28（68.3）	11（64.7）
透析アミロイドーシス（%）	6（14.3）*	0（0）	0（0）
悪性腫瘍（%）	2（4.8）	1（2.4）	2（11.8）
薬剤性（%）	1（2.4）	1（2.4）	0（0）
膠原病（%）	0（0）**	6（14.6）	3（17.7）
不明（%）	4（9.5）	5（2.4）	1（5.9）

#：結核 2 例（肺結核 1 例，粟粒結核 1 例）含む
*：血液透析 vs. その他 p＝0.004　**：血液透析 vs. その他 p＝0.009（±：SD）

生剤が有効であったなどの疑い症例を含め 20 例で起因菌として同定し得たものはメチシリン耐性黄色ブドウ球菌，緑膿菌，コアグラーゼ陰性ブドウ球菌，連鎖球菌であった．ウイルス性は 1 例で EB ウイルスであった．そのほかは非定型抗酸菌症 1 例，真菌性 2 例，不明 1 例，塗抹，培養，核酸増幅法によって結核と確定診断した症例を 2 例に認め，結核疑いで抗結核薬を使用した症例が 2 例であった．CKD stage 3～5 で細菌性は 24 例で，同定されたものは腸球菌，メチシリン耐性黄色ブドウ球菌，肺炎連鎖球菌であった．真菌症 1 例でクリプトコッカスネオフォルマンスを同定し，ウイルス性 2 例，不明 1 例であった．CKD stage 1～2 では細菌性が 8 例で同定されたものは腸球菌，緑膿菌であった．その他はウイルス性 2 例，不明 1 例であった．また，結核の疑いもあり，抗結核薬を使用した症例が 2 例あった．

血液透析の群では透析アミロイドーシスによる発熱を 6 例に認め，そのほかと比較し有意に高率（p＝0.0031）であった．診断はガリウムシンチでの集積や滑膜生検などで行った．部位は膝関節，股関節，肩関

節など多関節に及ぶ症例が多かった．また，透析アミロイドーシスと診断した症例は平均37.6±0.2℃と発熱の程度が比較的軽度であった．

悪性腫瘍と診断した症例は血液透析患者で2例（4.8%）でその内訳は胆嚢癌，胃癌であった．CKD stage 3～5では1例（2.4%）で成人T細胞白血病であった．CKD stage 1～2では2例（8.7%）で膵臓癌，胸腺腫瘍であった．

薬剤性が疑われた症例は全体で2例で，血液透析患者ではバンコマイシンが，stage 3～5の症例ではザイロリックが疑われた．

一方，膠原病関連疾患による発熱を示した症例は血液透析の群には認めず，その他と比較し有意に低値であった（p＝0.0094）．内訳はstage 3～5では結節性多発動脈炎，全身性エリテマトーデス，抗糸球体基底膜抗体腎炎，シェーグレン症候群，リウマチ性多発性筋痛症，慢性関節リウマチで，stage 1～2では原発性結節性紅斑，多発筋炎，成人Still病であった．

3．CKDの分類別の感染症の部位別の比較

表3に感染症の感染部位別分類を示す．血液透析の群では肺と上気道を合わせた気道感染による発熱の割合が27.6%ともっとも高値であった．また，血液透析の群でのみ腹膜炎，胸膜炎，心内膜炎による発熱を認めた．腹膜炎と診断した3例の全例において腹膜透析歴を認めた．また，血液透析の群においてそのほかの感染部位は腸管2例，四肢1例，脊椎1例，リンパ節1例，透析用のカテーテル感染を1例において認めた．またCKD stage 3～5ではそのほかの部位として腸管4例，髄膜1例，脊椎1例，胆嚢1例，CKD stage 1～2では腸管1例，髄膜1例であった．

4．透析歴別の不明熱の原因分類

表4に透析歴0～4年，5～14年，15～29年の3群に分け透析歴別の不明熱の原因分類を示した．すべての透析歴において感染症が原因の1位であった．15～29年の群では透析アミロイドーシスによる発熱が42.9%と高率に認めた．

5．血液透析患者における発熱の原因で分類した透析歴の比較

図に透析患者における発熱の原因と透析歴を示した．発熱の原因として透析アミロイドーシスと診断した症例の透析歴は平均23.1±5.0年，感染症は8.4±7.5年，悪性腫瘍は8.0±9.0年，薬剤性は1例で0.3年，不明は9.4±11.5年であった．アミロイドーシスが発熱の原因であった症例の透析歴はそれ以外が原因の症例に比較して有意に透析歴が長かった（p＜0.0001）．

6．発熱の原因別の検査結果

表6に血液透析患者における発熱の原因別の検査結果を示した．悪性腫瘍においてCRP，白血球，好中球が高値を示したが症例数が2例と少数で評価は困難で

表 4　感染症の感染部位別分類

Stage	血液透析	3～5	1～2
上気道・肺（%）	8（27.6）	8（28.6）	3（27.3）
腹膜（%）	3（10.3）	0（0）	0（0）
胸膜・心膜（%）	3（10.3）	0（0）	0（0）
尿路（%）	3（10.3）	9（32.1）	2（18.2）
その他（%）	6（20.7）	7（25.0）	2（18.2）
不明（%）	6（20.7）	4（14.3）	4（36.4）

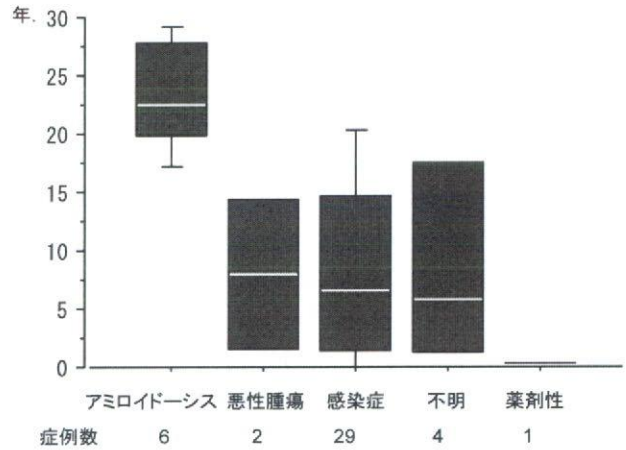

図　透析患者における発熱の原因と透析歴の関連

表 5　透析歴における発熱の原因

透析歴（年）	0～4	5～14	15～29
性別（男/女）	7/8	8/5	5/9
発熱の原因			
感染症（%）	11（73.3）	11（84.6）	7（50.0）
透析アミロイドーシス（%）	0（0）	0（0）	6（42.9）
悪性腫瘍（%）	1（6.7）	1（7.7）	0（0）
薬剤性（%）	1（6.7）	0（0）	0（0）
膠原病（%）	0（0）	0（0）	0（0）
不明（%）	2（13.3）	1（7.7）	1（7.1）

表 6　血液透析患者における発熱の原因別の検査結果

	症例数	CRP（mg/dL）	白血球数（/μL）	好中球数（/μL）	リンパ球数（/μL）
感染症	29	13.4±10.6	9,600±5,560	7,630±5,560	1,080±700
透析アミロイドーシス	6	11.5±8.1	6,690±4,420	5,140±3,750	970±610
悪性腫瘍	2	24.1±8.3	21,000±18,950	17,960±16,590	1,130±490
薬剤性	1	14.2	5,270	3,720	700
不明	4	4.3±4.4	8,240±1,600	5,390±1,030	1,460±570

あった．

Ⅲ．考　察

血液透析患者において，発熱の原因としては大別すると感染症，悪性腫瘍，膠原病，透析操作に伴う発熱，薬剤熱，透析アミロイドーシスなどがあげられる．

腎不全状態は顆粒球，リンパ球の機能低下を認め，免疫能低下状態にあり，易感染状態にある[2,3]．また，透析患者は皮膚の萎縮，汗腺の萎縮，および粘膜における気道の線毛運動の低下，肺胞マクロファージの機能低下，胃酸分泌の低下，消化管の潰瘍形成などの物理的障壁の異常が存在する[1]．したがって透析患者においてはシャントや種々のカテーテル留置が容易に細菌の侵入門戸となりやすい[2]．感染症は透析患者の合併症の中でも重要であり，2006年の日本透析医学会の調査によると，透析患者の死亡原因として感染症は心不全に次ぐ第二位で19.9%を占めている[5]．当院における原因不明の発熱で入院した患者において，感染症と診断した頻度は69.0%と最多であった．今回の検討では，発熱の原因が不明で入院した患者と対象を限定したためか，糸球体濾過量の保たれた比較的腎機能正常なCKD stage 1～2の患者とCKD stage 3～5や血液透析患者において発熱の原因としての感染症の頻度に差は認められなかった．感染の部位としては血液透析患者の症例で上気道，肺が最多であった．腹膜透析より血液透析に移行した症例において腹膜炎と診断した症例を3例認めた．腹膜透析歴のある患者は腹膜炎に注意が必要である．また，胸膜，心膜を熱源とした症例を3例認めたが，CKD stage 1～5では1例も認めず，透析患者において注意が必要である．尿路感染はすでに注意して鑑別されていたせいか，血液透析患者においては少なく，3例であった．一方，CKD stage 3～5の症例では9例と最多であった．血液透析患者特有の感染症としてシャント感染や透析用のカテーテル感染については，1例透析用カテーテルによる感染と診断した症例を認めた．

血液透析患者は上記のごとく易感染性があり，結核発症のハイリスクグループであり，その罹患率は一般の十数倍から数十倍といわれている[6]．それゆえ透析患者の感染の原因として結核の鑑別は重要である．透析患者の結核症の確定診断は困難なことが多く，診断的治療を要する症例も少なくない．われわれの検討で血液透析患者2例に塗抹，培養，核酸増幅法によって結核症と診断したが，CKD stage 1～5の患者においては1例も結核症の確定診断に至らなかった．

発熱の原因としての膠原病についてであるが，全身性エリテマトーデスは急速進行型で透析導入に至る症例では免疫活動性は高く，慢性腎炎腎不全例のような経過で腎不全に至る症例では，免疫学的活動性は乏しく透析導入後にはステロイドを中止することが可能な症例がある．今回のわれわれの検討では膠原病による発熱が血液透析患者に少なかった．

固形悪性腫瘍の発熱は，腫瘍の種類，発生部位によっても異なるが，一般に長期間持続する微熱が多く，ときに38℃以上になることもある．病期の進行につれて発熱の頻度は高くなり，遠隔転移ことに肝転移，また癌性腹膜炎や胸膜炎を合併すると発熱をみることが多い[7]．悪性腫瘍は血液透析患者において2例に認め，常時医療機関で維持透析をうけ管理されているとはいえ，常に疑いをもつ必要がある．

透析アミロイドーシスは長期透析患者に合併する疾患で長期透析患者の骨，軟骨，滑膜など骨関節組織にアミロイドが沈着することにより，手根管症候群，破壊性脊椎関節症および嚢胞性骨病変などの骨関節障害を発症する．透析アミロイドーシスではアミロイド沈着局所において，advanced glycation end products化β_2-ミクログロブリンにマクロファージが遊走し，receptorを介して活性化され，サイトカインを放出して，炎症反応が進展するという機序が提唱されている[6]．今回6例にアミロイドーシスによる発熱を認めた．透析歴は平均23.1±5.0年（16～29年）でそのほかの原因による発熱に比較して有意に長期であった（$p<0.0001$）．透析歴15年から29年の患者においては42.9%と高率に認めた．本件検討では透析アミロイドーシスと診断した症例では平均37.6±0.2℃と発

熱の程度は比較的軽度であった．ガリウムシンチでの集積は膝部，股関節，肩関節痛といった四肢の関節が多かった．長期透析患者においてアミロイドーシスによる発熱も鑑別として考える必要がある．

血液透析患者において透析操作に伴う発熱は今回の検討では認めず，薬剤熱は1例に認めた．

今回の検討において血液透析症例はCKD stage 1～2の症例と比較してCRPが高値であったにもかかわらず，白血球数は有意差を認めず，リンパ球はむしろ減少していた．腎不全患者の細胞性免疫能ではリンパ球の減少が報告されている[8]．今回の検討での血液透析患者でのCRPの高値，リンパ球の低下の原因は不明で，各群で発熱の原因に偏りがあり症例数も少なく，CKDのstage別でのCRP，白血球数に関しては症例を増やし発熱の原因など条件をそろえ検討する必要がある．

血液透析患者において発熱の原因別でCRP，白血球などの採血結果の検討を行ったが，症例が少なく，また，感染症のなかでも細菌性，ウイルス性などで分類し，症例を増やし検討する必要がある．

今回の検討の限界としては，今回の検討は原因不明の発熱で入院した患者を対象としており，ウイルス性の感冒などで入院せずに改善した患者や，起炎菌不明の肺炎で入院した患者が肺結核症であったなど，あらかじめ診断名のついた患者は対象外としている点など，一般の発熱の原因を反映しているわけではない．また，当科が腎専門のため，CKDの分類のいずれにも当てはまらない腎機能障害のない患者の検討はできなかった．

結　語

血液透析患者において原因不明の発熱を認めた際，まず頻度が多く，治療が遅れた場合，致命的となりうることから感染症を疑うべきである．また，結核の可能性，透析歴の長い場合は透析アミロイドーシスに注意が必要である．

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Characteristics of dialysis-related amyloidosis in patients on haemodialysis therapy for more than 30 years

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Abstract

Background. Dialysis-related amyloidosis is one of the chronic the complications of haemodialysis. We conducted an investigation of dialysis-associated amyloidosis in extremely long-term survivors.

Methods. Twenty-one patients on haemodialysis for more than 30 years ('30+' group) and 13 patients on haemodialysis for 20–30 years ('20–30' group) at Sangenjaya Hospital were enrolled in this study. The frequencies of operations for conditions related to haemodialysis-related amyloidosis were examined.

Results. The mean age at the start of haemodialysis was younger in the '30+' group (29.1 ± 7.3 years) than in the '20–30' group (40.5 ± 8.2 years, $P = 0.0003$). Eighteen (85.7%) patients had undergone surgery for CTS, six (28.6%) had undergone surgery for trigger finger and six (28.6%) had undergone surgery for cervical destructive spondyloarthropathy (DSA) at 30 years after the start of haemodialysis therapy. Patients who were over the age of 30 years at the start of dialysis therapy more frequently underwent CTS operations (100%) than those who were under 30 years of age at the start of dialysis (76.9%; $P = 0.025$) in the '30+' group at 30 years after the start of haemodialysis. The frequencies of operations for CTS did not differ significantly between the '20–30' group and the '30+' group.

Conclusions. Haemodialysis-associated amyloidosis was common in extremely long-term survivors. Even though the mean age at the start of haemodialysis was younger in the '30+' group than in the '20–30' group, the frequency of operations for CTS did not differ. This may be attributable to the recent advances in haemodialysis technologies.

Keywords: amyloidosis; carpal tunnel syndrome; destructive spondyloarthropathy; high-flux membrane; long-term haemodialysis

Introduction

Since its experimental introduction in 1960, haemodialysis has become a widely performed and relatively safe procedure. Therapeutic strategies have been developed, and the number of extremely long-term survivors of haemodialysis therapy has been increasing. Because there are not enough renal transplantation donors in Japan, the duration of haemodialysis therapy is much longer than in other countries [1], and regional differences in the mortality rates of haemodialysis patients have been found highest in the United States and lowest in Japan [1,2]. Therefore, Japan provides an ideal setting for describing patients receiving extremely long-term dialysis. We have previously reported various indexes affecting mortality in patients who have received haemodialysis for more than 30 years [3]. Dialysis-related amyloidosis is one chronic complication of long-term haemodialysis that affects quality of life. Almost no previous reports have discussed amyloidosis in patients receiving maintenance haemodialysis for more than 30 years. In 1985, β2-microglobulin (β2-m), with a molecular weight of 11.800 Da, was identified as the major constituent protein of this amyloid [4]. Since then, haemodialysis technology for dialysis-related amyloidosis has been developed. In the present study, we investigated dialysis-associated amyloidosis in patients receiving maintenance haemodialysis for more than 30 years.

Subjects and methods

Twenty-one patients who had been receiving haemodialysis for >30 years ('30+' group) at Sangenjaya Hospital as of 1 July 2008 were enrolled in this study. Reverse osmosis treatment for dialysis water was initiated at our hospital in 1988, and the use of high-flux membranes was started at about the same time. To compare histological differences, 13 patients receiving haemodialysis for 20–30 years ('20–30' group) were also studied.

Background data (age, gender, cause of renal failure) and the medical histories of operations performed

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for haemodialysis-associated amyloidosis [such as carpal tunnel syndrome (CTS), cervical destructive spondyloarthropathy (DSA), trigger finger and amyloid-filled bone cysts in the femoral neck area] were collected from the patient records at our hospital. The serum levels of C-reactive protein (CPR) and albumin and the use of erythropoiesis-stimulating agents (ESA) were also examined as parameters of malnutrition and inflammation.

Patients were divided according to gender and age as of the start of dialysis therapy (30 years and over, and under 30 years). The Kaplan–Meier test was used to estimate the history of operation and a log-rank test was used to compare the history of operations between the two groups. The Student *t*-test was used to compare continuous variables between the two groups. The chi-square or Fisher exact probability test was applied for categorical data. Data values are presented as the means ± SD. A probability of <0.05 was considered significant. All statistical calculations were performed using Stat View SE.

Results

Background characteristics of the long-term haemodialysis patients

Table 1 shows the characteristics of the patients, age, gender and the primary cause of their end-stage kidney disease (ESKD). Mean age was 62.5 ± 6.8 in the '30+' group and 65.2 ± 7.1 in the '20–30' group. Mean age at the start of haemodialysis was younger in '30+' group (29.1 ± 7.3) than in '20–30' group (40.5 ± 8.2, $P = 0.0003$). The mean duration of haemodialysis was 33.4 ± 1.9 years in the '30+' group years and 24.7 ± 3.4 in the '20–30' group. Out of 21 patients, 14 patients were male (66.7%) in the '30+' group. All of their primary cause of ESKD was chronic glomerular nephritis in the '30+' group, and all except one patient whose cause of ESKD was diabetic nephropathy was also chronic glomerular nephritis in '20–30' group. Five patients (23.8%) were treated with HDF in the '30+' group and five patients (38.5%) in '20–30' group. The serum level of CRP tended to be higher and that of albumin tended to be lower in the '30±' group than in the '20–30' group, but the difference was not statistically significant. The rate of use of ESA tended to be higher in the '30+' group than in the '20–30' group, but this difference was also not statistically significant.

Operations for amyloidosis

Figure 1 shows the history of operations performed for CTS. Endoscopic carpal tunnel release was performed instead of conventional open carpal tunnel release after 1986. Among the 21 patients in the '30+' group, 17 (81.0%) underwent operations for CTS at 30 years after the start of haemodialysis therapy (Figure 1a). No gender differences (Figure 1b) were observed. Patients who were 30 years and over at the start of their dialysis therapy underwent CTS operations more frequently than those who were under 30 years at the start of haemodialysis (100% versus 76.9%, respectively; $P = 0.025$, Figure 1c).

Figure 2 shows the history of operations performed for cervical DSA (decompression and fixation). Among the 21 patients in the '30+' group, 6 (28.6%) underwent operations for cervical DSA at 30 years after the start of haemodialysis therapy (Figure 2a). No gender differences (Figure 2b) were observed. Patients who were 30 years and over at the start of their dialysis therapy underwent operations for cervical DSA more frequently than those who were under 30 years at the start of haemodialysis (62.5% versus 7.7%, respectively; $P = 0.003$, Figure 2c).

Figure 3 shows the history of operations performed for trigger finger and amyloid- filled bone cysts in the femoral neck area. Releasing the A1 pulley was performed for trigger finger, while a bipolar hemiarthroplasty was performed

Table 1. Background information

Duration of haemodialysis	20–30 years	Over 30 years	*P*-value
Number	13	21	
Age	65.2 ± 7.1	62.5 ± 6.8	NS
Age at the start of HD	40.5 ± 8.2	29.1 ± 7.3	0.0003
Duration of HD (years)	24.7 ± 3.4	33.4 ± 1.9	<0.0001
Gender			
Men	8 (61.5%)	14 (66.7%)	NS
Women	5 (38.5%)	7 (33.3%)	NS
Cause of ESKD			
Chronic glomerulonephritis	12 (92.3%)	21 (100%)	NS
Diabetic nephropathy	1 (7.7%)	0 (0%)	NS
Method of haemodialysis			
HD	8 (61.5%)	16 (76.2%)	NS
HDF	5 (38.5%)	5 (23.8%)	NS
Parameters of malnutrition and inflammation			
CRP (mg/dl)	0.16 ± 0.08	0.33 ± 0.46	NS
Albumin (g/dl)	3.9 ± 0.2	3.8 ± 0.3	NS
Use of ESA (%)	69.2	85.7	NS

ESKD: end-stage kidney disease, CRP: C-reactive protein, ESA: erythropoiesis-stimulating agents, HD: haemodialysis, HDF: haemodiafiltration. Mean ± SD.

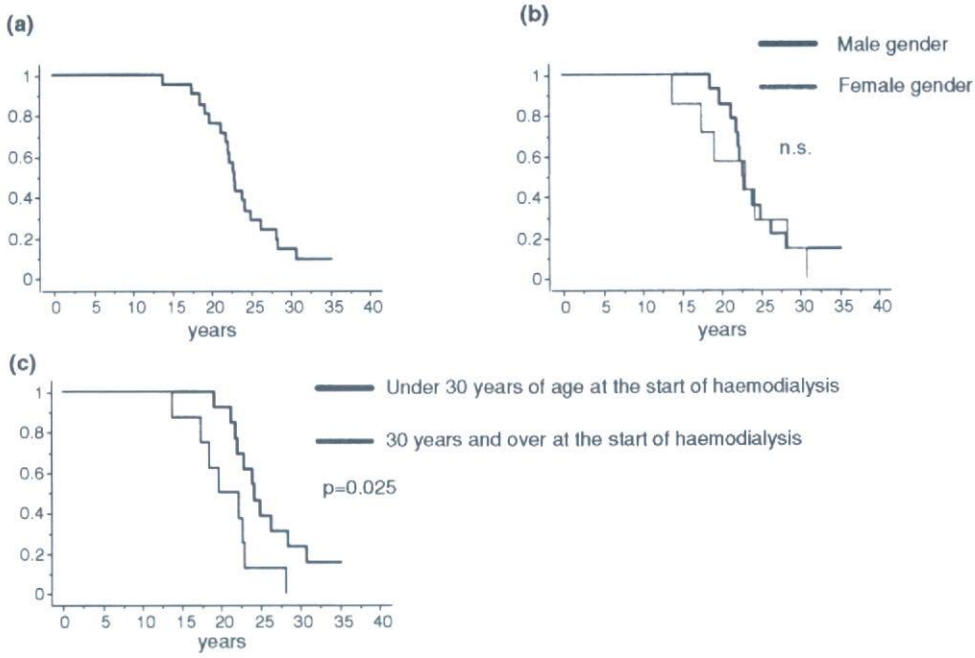

Fig. 1. History of operations for carpal tunnel syndrome (CTS). (a) Overall patients (b) divided according to gender, (c) divided according to age at the start of HD.

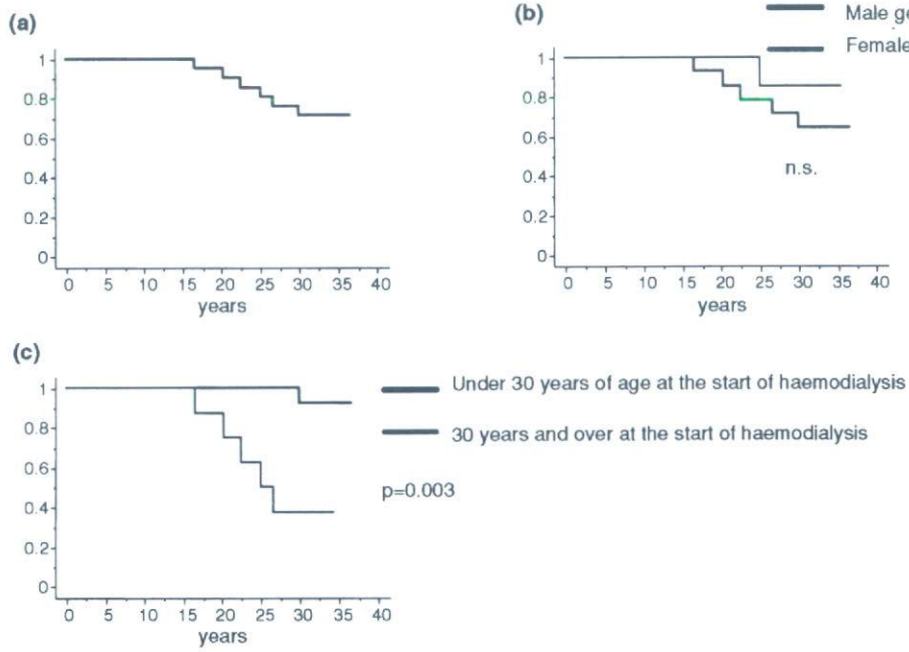

Fig. 2. History of operations for cervical destructive spondyloarthropathy (DSA). (a) Overall patients, (b) divided according to gender, (c) divided according to age at the start of HD.

for amyloid-filled bone cysts in the femoral neck area. Among the 21 patients in the '30+' group, 6 (28.6%) had undergone operations for trigger finger at 30 years after the start of haemodialysis therapy (Figure 3a). Among the 21 patients in the '30+' group, 4 (19.0%) had undergone operations for amyloid-filled bone cysts in the femoral neck area at 30 years after the start of haemodialysis therapy (Figure 3b).

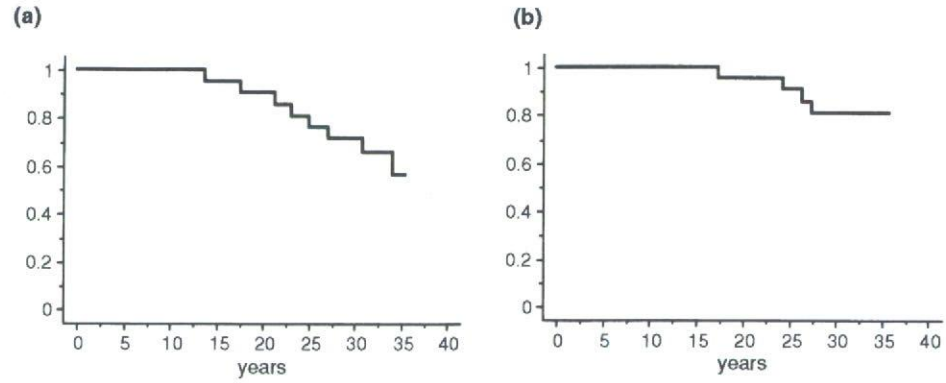

Fig. 3. History of operations for other amyloidosis-related diseases. (a) Operations for trigger finger, (b) operations for amyloid-filled bone cysts in the femoral neck area.

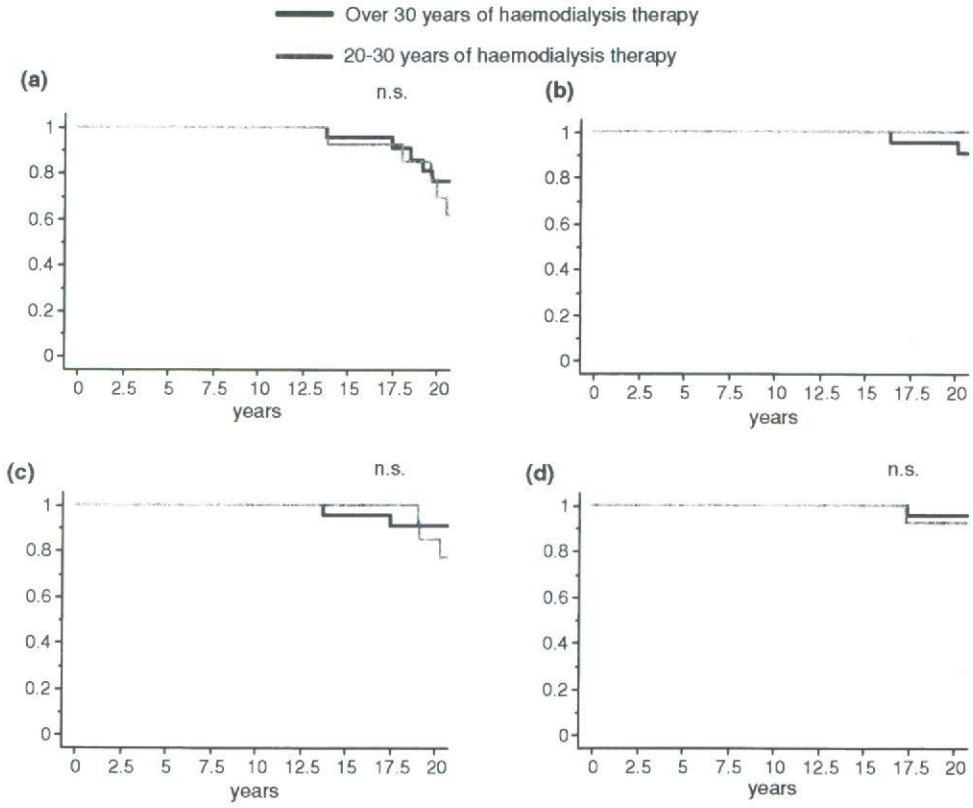

Fig. 4. Comparison of the history of operations for amyloidosis between haemodialysis for over 30 years and for 20–30 years' age groups. (a) Operations for carpal tunnel syndrome, (b) operations for cervical destructive spondyloarthropathy, (c) operations for trigger finger, (d) operations for amyloid-filled bone cysts in the femoral neck area.

Figure 4 compares the operation histories for amyloidosis in the '30+' and '20–30' groups. No statistical differences were found between '30+' group and '20–30' group with regard to operations for CTS (23.8% versus 23.1%, respectively), trigger finger (9.5% versus, 15.4%, respectively) or amyloid-filled bone cysts in the femoral neck area (4.8% versus 7.7%, respectively) at 20 years after the start of haemodialysis therapy. None of the patients in the '20–30' group had undergone an operation for cervical DSA at 20 years after the start of haemodialysis therapy.

We compared patients in whom haemodialysis had been started over the age of 40 years. Patients in the '30+' group underwent operations for CTS more frequently than those in