Hemodialysis‐related amyloidosis: Is it still relevant?

doi: 10.1111/sdi.12720

Hemodialysis-Related Amyloidosis: Is It Still Relevant?

Shuzo Kaneko and Kunihiro Yamagata

Department of Nephrology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Address correspondence to: Kunihiro Yamagata,MD,PhD, Department of Nephrology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8577, Japan
Tel:+81-298-53-3202; Fax:+81-298-53-3202; E-mail: k-yamaga@md.tsukuba.ac.jp

Word counts: Abstract 262words, body of manuscript 2629words

ABSTRACT:
Accumulation of amyloid fibrils from β2_microglobulin (β2M) was first recognized as a characteristic osteoarticular complication in long-term hemodialysis (HD) patients and called “HD-related amyloidosis” (HRA). However, this syndrome can also be observed in end-stage renal diseases (ESRD) patients undergoing peritoneal dialysis, and even in patients with chronic renal failure *before* the initiation of dialytic therapy, suggesting that HD is not a direct cause but that accumulation of β2M or some β2M-associated molecules in the body is a common pathogenesis. Currently the term “dialysis-related amyloidosis” (DRA) is widely used for β2M-amyloid (Aβ2M) amyloidosis associated with ESRD, though DRA patients consist mostly of those undergoing long-term HD.
Factors other than β2M accumulation also play a role in the formation/local deposition of Aβ2M and disruption of tissue architecture. Conformational changes of β2M by misfolding/unfolding, and promoting/inhibitory effects induced by other co-existing molecules, advanced glycation and oxidation, and direct cell toxicity have also been documented.
Two technological improvements of HD have been the keys to prevent the development and progression of DRA: the efficient removal of β2M by using high-flux membranes, high-volume convection and adsorptive column/membrane, as well asthe use of biocompatible membranes and

dialysates (e.g. ultrapure and acetate-free dialysates) which have the minimized both inflammation and β2M production.
Epidemiologically, a decrease in the incidence of DRA has recently been reported; however, longer survival of HD patients may contribute to the development of more DRA, though with a delayed onset. In this article, we describe the pathogenesis of DRA, the strategies developed for its prevention and minimization, and the favorable epidemiological data achieved by these efforts.

Introduction

Hemodialysis (HD)/dialysis-related amyloidosis (HRA/DRA) is a systemic amyloidosis that is mainly associated with osteoarticular lesions, including carpal tunnel syndrome (CTS), trigger finger (TF), spinal canal stenosis (SCS), destructive spondyloarthropathy (DSA), joint arthropathy and bone cysts. In 1975, Warren and Otieno reported a high incidence of CTS in HD patients (1); then, in 1980, amyloid deposition was recognized as being associated with CTS (2). In 1984, Kuntz et al reported DSA in HD patients (3). In 1985, Charra et al reported shoulder pain with amyloid deposition as well as CTS in long-term HD patients (4); in the same year, beta2-microglobulin (β2M) was identified as the precursor protein of amyloid by Gejyo *et al* (5).

Although β2M-amyloidosis (Aβ2M) had been observed in patients undergoing peritoneal dialysis, and even in patients with chronic renal failure before the initiation of dialytic therapy (6-8), HRA was recognized as a characteristic complication of long-term HD in the earlier era of HD which used low-flux membranes (i.e., cellulosic membranes such as cuprophan) with low biocompatibility of both the membrane and the dialysate. Currently the term DRA is widely used for all Aβ2M associated with end-stage renal diseases (ESRD), even though almost all DRA patients do undergo long-term HD. The removal of β2M from the body is almost wholly dependent on kidney function (5); therefore, greatly elevated circulating β2M in ESRD patients with disrupted kidney function is a prerequisite for developing DRA.
Over the last two decades, even though the reduction of serum β2M level has not reached ideal levels, technological improvement of HD (i.e., high-flux membrane, high-volume convection and ultrapure dialysate (UPD))

has certainly contributed to delay the onset of DRA and reduced its incidence and prevalence (9,10) (Fig. 1), which may in turn explain the observation that the most certain cause of DRA onset is a long dialysis vintage (10-12).
In this article, we describe the pathogenesis of DRA, and the evidence of strategies (i.e., technical improvements in HD) that have succeeded in reducing DRA from the past up to today. We then discuss the current epidemiological data and factors associated with DRA.

Pathogenesis of DRA: retention of β2M and amyloid fibril formation

β2M forms the beta chain of human leukocyte antigen (HLA) on all nucleated cells and is the causative protein of HRA/DRA. The production rate of β2M is constant, but increases in inflammation, infection and lymphoproliferative disorders. Most β2M can be removed by glomerular filtration and subsequent reabsorption and catabolism by proximal tubules. β2M accumulates when the removal rate falls below the production rate in ESRD patients, with serum β2M levels increasing up to 60-fold (5).

Factors other than a high circulating level of β2M also play a role in the formation/local deposition of Aβ2M and disruption of tissue architecture. In *in vitro* studies, nucleation-dependent polymerization followed by an elongation process is required for Aβ2M formation. Conformational change by unfolding/misfolding of β2M is considered a first rate-determining step. Motomiya et al reported that β2M fragments having C-terminal unfolding, including a fragment lacking the first six amino acids (ΔN6β2M) (13), which has been recognized as an important amyloidogenic form, are essential for amyloidogenesis (14). Hereditary systemic amyloidosis due to the Asp76Asn-β2M variant—a new type of Aβ2M with normal renal function—also suggests the importance of conformational change for β2M amyloidogenesis (15). Naiki and coworkers (16,17), and other researchers (18) identified numerous promoters (i.e., type 1,2 collagen, glycosaminoglycan including heparin, proteoglycan, apolipoprotein E, lysophospholipid, free fatty acids and pentraxins (serum amyloid P component and C-reactive protein) and inhibitors (i.e., α2 macroglobulin and haptoglobin)) of Aβ2M formation and elongation in *in vitro* studies.

For tissue damage caused by Aβ2M deposition, advanced glycation end-products and advanced oxidation protein products, partially co-located on Aβ2M in uremic states, have been reported to induce proinflammatory effects; these are assumed to be triggered by bio-incompatible dialysis and contaminated dialysate. Recently, a new mechanism of direct cytotoxicity, by which endocytosed Aβ2M induced necrosis and apoptosis by disrupting endosomal/lysosomal alteration of membranes in synovial fibroblasts, was reported (19).

Extracorporeal β2M removal in hemodialysis patients

In the first two decades after HRA/DRA was first recognized in 1980, substantial technological improvements of HD in both permeability and biocompatibility of membranes and convection were made, especially in terms of satisfactory removal of circulating β2M. However, in the current era, the reduction of serum β2M has still not reached ideal levels. Renal transplantation is the ultimate option for bringing serum β2M close to a normal range with dramatic improvement of DRA symptoms, although radiologic (bone cysts) and histologic lesions do not disappear after long-term follow-up (20).

High-flux membrane

Unmodified cellulosic membranes, such as cuprophane which is both impermeable and has low adsorptivity for β2M, have been recognized as a major direct culprit of HRA development. By contrast, high-flux membranes remove β2M at high rates and reduce early DRA onset in HD patients (12, 21-24).

Membrane biocompatibility is assumed to be brought about by the adsorption characteristics of its materials. Indeed, adsorbed β2M amounts vary considerably depending on the material: namely, polymethylmethacrylate (PMMA) > polyacrylonitrile (PAN/AN69) > polysulfone (PS), polyester-polymer-alloy (PEPA) and cellulose-triacetate (CTA) (24). However, judging from the remarkable difference of β2M clearance between high-cut-off (cutoff 50–60 kDa) HD and conventional high-flow (cutoff 15–20 kDa) HD (25), the differences in sieving seem to be even more important for removal rates.

Convective therapy

In a retrospective study of more than 6000 individuals with a median

observation period of about 2 years, Locatelli et al documented the superiority of convection (i.e., hemofiltration (HF) and hemodiafiltration (HDF)) compared to diffusion (i.e. conventional HD) in decreasing DRA morbidity and delaying the need for CTS surgery (26). Currently, several convective modalities (i.e., pre-/post-/mid- dilution HDF, on-line-/off-line HDF, pull and push HDF, double high-flux HDF) are available; additionally, high-flux HD and intermittent infusion HDF can be considered forms of "low-volume HDF", in which convective exchange occurs via internal back-filtration within the dialyzer. All these modalities can remove β2M with great success compared with low-flux HD. Thus, the major determinants of β2M removal per session are membrane permeability, duration of treatment, and convective volume (27). Furthermore, the effective lowering of serum β2M levels by HDF as compared with low-flux HD is more prominent in patients without (vs. with) residual renal function (28).
In recent decades, the targets of convective therapies have shifted to the removal of small proteins or protein-binding uremic toxins which are larger than β2M. Several randomized control trials (RCTs) studying, e.g., high-flux versus low-flux (29-31) HD, HDF versus HD, and higher- versus lower-volume HDF, have shown certain favorable results for convective therapies and their higher volume in preventing erythropoietin-stimulating agent resistance, endothelial dysfunction, insufficient management of serum phosphate, intradialytic hypotension (32-34), as well as in reducing cardiovascular events/death and improving survival (35-40); meanwhile, there are no noteworthy prospective RCTs designed to examine the effect of convective therapies on the outcome of DRA.

A few postmortem studies have shown that Aβ2M deposits in long-term HD patients are not specific to osteoarticular tissue; the main other organs involved have been the vascular walls, the heart, gastrointestinal tract and lungs (41). In the latest version of amyloid classification by the Nomenclature Committee of the International Society of Amyloidosis, the type of Aβ2M associated with DRA was modified from 'localized' to 'systemic' (42).
The hypothesis that β2M deposition, particularly in the blood vessels and heart, would also incite specific processes with pathogenic effects in the

absence of extensive Aβ2M deposition was suggested in a review article (27). Indeed, this hypothesis explains the fact of favorable cardiovascular outcomes of higher convective therapy in patients even with relatively short dialysis periods compared to that of DRA onset. On the other hand, Uji et al demonstrated that a few intermediate forms of β2M, which were revealed by capillary electrophoresis, returned from the tissues and increased in the serum even after the use of online HDF treatments, suggesting that amyloidogenic β2M forms still cannot be removed by the current higher convective therapy (43).

Intensive therapy

Intensive regimens including nocturnal HD (8 hours, six night/week) and daily hemofiltration with high-flux membranes can remove 5- to 8-fold more β2M than conventional HD and decrease serum β2M levels significantly. Nevertheless, serum levels in these treatments do not reach the normal range (44, 45). Although a recent meta-analysis showed lower systolic blood pressure, increased hemoglobin levels and lower serum phosphate level in patients undergoing nocturnal HD compared with those undergoing conventional HD (46), there have been no RCTs examining the effect of intensive therapy on DRA outcomes.

β2M-adsorptive apheresis

A β2M-adsorbent column, Lixelle, which connects to a dialyzer in tandem for direct hemoperfusion for DRA, became commercially available in Japan in 1996, in Europe in 2013 and in USA in 2015. The inside of the column is composed of porous cellulose beads with a hydrophobic hexadecyl chain as a ligand. The determinants of the adsorption are both size and hydrophobicity; therefore, any hydrophobic molecule weighing 4,000–20,000 g/mol can be adsorbed in the column; indeed, β2M (molecular weight 11,800 g/mol) is highly adsorbed . The column adsorbs various other molecules as well as β2M: numerous inflammatory cytokines (47), microbial fragments such as endotoxins and peptidoglycans, free light chains, myoglobin, bilirubin and drugs (digoxin, antibiotic agents); therefore, a synergistic effect of β2M elimination and anti-inflammatory effects is assumed.

Treatments with Lixelle have been reported to be effective for improving both subjective symptoms, including joint pains and stiffness and activities

of daily living (48-52), and objective findings such as pinch strength and the median motor terminal latency (48). Furthermore, decrease or arrest of bone cyst formation with significant β2M clearance was also reported (49, 51); however, these studies were conducted in small numbers of patients and were evaluated at an early point within short-period treatments of 1–2 years. Gejyo reported the results of a Japanese nationwide questionnaire survey from 345 patients who had used Lixelle; the mean durations of dialysis and Lixelle treatment were 25.9 ± 6.2 years and 3.5 ± 2.7 years, respectively. Based on self-evaluation by patients, the worsening of symptoms was inhibited in 84.9–96.5%, suggesting that Lixelle treatment improved symptoms or prevented the progression of DRA in most patients (52).

In the health insurance system in Japan, Lixelle cannot be used with HDF. From several case reports in Japan, even though the β2M removal rate was equivalent, HD with Lixelle was superior to convective therapy including online HDF and pull and push HDF in relieving joint pain. There are no RCTs comparing the effect of Lixelle with that of higher convective therapy; however, there may be differences in clinical indication between the two therapies. According to previous reports and expert opinions, Lixelle should be used in patients with severe joint symptoms, and/or in patients who have contraindications for higher convective therapy, such as those who are elderly, have malnutrition or chronic inflammation. In the latter case, the usage of low-flux and biocompatible membranes (i.e., PMMA and AN) are recommended.

Prevention of inflammation and β2M production during hemodialysis
Membrane biocompatibility
Bioincompatible membranes such as cuprophane cause complement activation, followed by gene expression of inflammatory cytokines in peripheral blood cells (53). Evidence from both *in vitro* and *in vivo* studies suggests that cuprophane induces excessive β2M production(54, 55). Although these findings are not consistent (56), low-flux cuprophane membranes are the most permeable to pyrogens from dialysate (57), which stimulates inflammation, leading to excessive β2M production.
Dialysate

Regarding the biocompatibility of the dialysate, elimination of acetate and sterilization have been two important issues. Acetate-containing dialysate can induce inflammatory cytokine production, peripheral vasodilatation, and suppression of myocardial function, resulting in intradialytic hypotension in HD patients. Several small-scale RCTs have been conducted and have discussed these symptoms, although their conclusions varied. Metabolic acidosis and higher plasma β2M levels were observed in HD patients using acetate-containing dialysate compared with bicarbonate-containing dialysate. Metabolic acidosis may be relevant to DRA. In normal men, NH_4Cl loading increases β2M mRNA expression in lymphocytes (58).

The use of ultrapure dialysate (UPD), one with almost no bacteria or endotoxins, as an important issue in the current era of highly convective therapy. In 226 long-term HD patients with cellulosic membranes, the prevalence of CTS onset was significantly lower in patients with UPD compared with non-UPD (59). Several studies have also demonstrated that the use of UPD correlates with a decrease of DRA (23 ,60). A recent meta-analysis concluded that the use of UPD in HD patients decreased markers of inflammation and oxidative stress, increased serum albumin and hemoglobin and decreased erythropoietin requirement (61); however, there is no information on DRA onset in this study.

Current epidemiology of DRA

There are two reports demonstrating that the prevalence of DRA has considerably decreased (9,10). In a single-center study from Germany in 1997, Schwalbe et al reported the prevalence of DRA in 1988 versus 1996 (9); randomly selected patients studied in 1988 were matched by time on HD (mean 71 months, range 3 to 207) and age (mean 51 years, range 22 to 80) with patients of the 1996 population. Compared to the 1988 population, the 1996 population exhibited significantly lower prevalence of DRA in both CTS (1/43 vs 7/43) and bone cysts (positive patients, 3/43 vs. 13/43; possible sites, 7/272 33/272), and less home HD and more frequent usage of reverse osmosis water with bicarbonate buffer than acetate for dialysate preparation. No difference in serum β2M levels between the two groups was evident, and the proportion of time occupied by high-flux synthetic membranes usage in total dialysis time was quite low in both groups (13%

of 1996 and 6% of 1988). The author speculated that β2M removal is unlikely to be the source of the remarkable decrease of DRA, and that other factors, for example, dialysate composition and purity, may be involved.

Recently, we documented the updated epidemiology of DRA based on the national registry data from Japanese Society for Dialysis Therapy (JSDT) (10). We retrospectively compared the incidence of first-time CTS surgery as a proxy for DRA onset in 1998 (n=36,489) versus 2010 (n=166,237) cohorts (Fig. 1). The incidence of first-time CTS surgery was significantly higher in the 1998 cohort than in the 2010 cohort (1.77% versus 1.30%, adjusted OR 2.22 (1.68-2.95)). This favorable result of the 2010 cohort compared with the 1998 cohort was most prominent in patients with longer dialysis periods, younger age and lower pre-HD β2M (Fig. 2). Using this 2010 cohort, we showed that other factors associated with CTS besides dialysis duration were age, gender, serum albumin, and diabetic nephropathy. We also indicated that β2M clearance >80% may contribute to decrease the incidence of CTS (62) (Fig. 3).

According to the latest Japanese national registry data from JSDT at the end of 2016, the prevalence of dialysis patients who used Lixelle or another adsorptive dialyzer (i.e., AN69 membranes) was only 0.43% (1,355/318,814). However, as dialysis vintage increased, the value increased; 1.8 (230/12,484), 4.1 (284/6,897), 8.0 (317/3,987), 10.3 (222/2,152), and 11.5% (91/793) for dialysis vintage of 20-25, 25-30, 30-35, 35-40, and ≥40 years, respectively.

Although long-term survival of HD patients may increase the incidence of delayed onset DRA, the technological improvement of HD certainly has decreased the incidence of early onset DRA.

Conclusions

The great success of HD in removing β2M (or some β2M-associated molecules) seems to be a major contributor to the delay of DRA onset, but this is still a controversial hypothesis. Again, DRA is a disease that develops only in ESRD patients in whom β2M has accumulated remarkably in the body. Even if serum β2M levels cannot be lowered, better removal of β2M can inhibit irreversible deposition into tissues by maintaining a dynamic equilibrium between the serum and tissue. Additionally, the improved biocompatibility of both membranes and

dialysates minimizes β2M production and inflammation, which could also help prevent the development and progression of DRA.

References

1. Warren DJ, Otiento LS. Carpal tunnel syndrome in patients on intermittent haemodialyis. *Postgrad Med J*. 1975; 51: 450-452.
2. Assenat H, Calemard E, Charra B, Laurent G, Terrat JC, Vanel T. Hemodialysis: carpal tunnel syndrome and amyloid substance *Nouv Presse Med.*1980; 9: 1715.
3. Kuntz D, Naveau B, Bardin T, Drueke T, Treves R, Dryll A. Destructive spondylarthropathy in hemodialyzed patients. A new syndrome. *Arthritis Rheum.* 1984; 27: 369-375.
4. Charra B, Calemard E, Uzan M, Terrat JC, Vanel T, Laurent G. Carpal tunnel syndrome, shoulder pain and amyloid deposits in long-term haemodialysis patients. *Proc Eur Dial Transplant Assoc Eur Ren Assoc.* 1985; 21: 291-295.
5. Gejyo F, Yamada T, Odani S, et al. A new form of amyloid protein associated with chronic hemodialysis was identified as beta 2-microglobulin. *Biochem Biophys Res Commun.* 1985; 129: 701-716.
6. Gagnon RF, Lough JO, Bourgouin PA: Carpal tunnel syndrome and amyloidosis associated with continuous ambulatory peritoneal dialysis. *CMAJ.* 1988; 139: 753-755.
7. Benz RL, Siegfried JW, Teehan BP. Carpal tunnel syndrome in dialysis patients: comparison between continuous ambulatory peritoneal dialysis and hemodialysis populations. *Am J Kidney Dis.* 1988; 11: 473-476.
8. Zingraff JJ, Noel LH, Bardin T, et al. Beta 2-microglobulin amyloidosis in chronic renal failure. *N Engl J Med.* 1990; 323: 1070-1071.
9. Schwalbe S, Holzhauer M, Schaeffer J, Galanski M, Koch KM, Floege J: Beta 2-microglobulin associated amyloidosis: a vanishing complication of long-term hemodialysis? *Kidney Int.* 1997; 52: 1077-1083.
10. Hoshino J, Yamagata K, Nishi S, et al. Significance of the decreased

risk of dialysis-related amyloidosis now proven by results from Japanese nationwide surveys in 1998 and 2010. *Nephrol Dial Transplant.* 2016; 31: 595-602.

11. Jadoul M, Garbar C, Noël H, et al. Histological prevalence of beta 2-microglobulin amyloidosis in hemodialysis: a prospective post-mortem study. *Kidney Int. 1997;* 51: 1928-1932.
12. Van Ypersele de Strihou C, Jadoul M, Malghem J, Maldague B, Jamart J. Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. *Kidney Int.* 1991; 39: 1012-1019.
13. Esposito G, Michelutti R, Verdone G, et al. Removal of the N-terminal hexapeptide from human beta2-microglobulin facilitates protein aggregation and fibril formation. *Protein Sci.* 2000; 9: 831-845.
14. Motomiya Y, Higashimoto Y, Uji Y, Suenaga G, Ando Y. C-terminal unfolding of an amyloidogenic β2-microglobulin fragment: ΔN6β2-microglobulin. *Amyloid.* 2015; 22: 54-60.
15. Valleix S, Gillmore JD, Bridoux F, et al. Hereditary systemic amyloidosis due to Asp76Asn variant β2-microglobulin. *N Engl J Med.* 2012; 366 : 2276-2283.
16. Naiki H, Yamamoto S, Hasegawa K, Yamaguchi I, Goto Y, Gejyo F. Molecular interactions in the formation and deposition of beta2-microglobulin-related amyloid fibrils *Amyloid.* 2005; 12: 15-25.
17. Ozawa D, Hasegawa K, Lee YH, et al. Inhibition of beta2-microglobulin amyloid fibril formation by alpha2-macroglobulin. *Biol Chem.* 2011; 286: 9668-9676.
18. Sultan A, Raman B, Rao ChM, Tangirala R. The extracellular chaperone haptoglobin prevents serum fatty acid-promoted amyloid fibril formation of β2-microglobulin, resistance to lysosomal degradation, and cytotoxicity. *J Biol Chem.* 2013; 288 : 32326-32342. doi: 10.1074/jbc.M113.498337.
19. Okoshi T, Yamaguchi I, Ozawa D, Hasegawa K, Naiki H. Endocytosed 2-Microglobulin Amyloid Fibrils Induce Necrosis and Apoptosis of Rabbit Synovial Fibroblasts by Disrupting Endosomal/Lysosomal Membranes: A Novel Mechanism on the Cytotoxicity of Amyloid Fibrils. *PLoS One.* 2015 Sep 30;10(9):e0139330. doi: 10.1371/journal.pone.0139330.

20. Küchle C, Fricke H, Held E, Schiffl H. High-flux hemodialysis postpones clinical manifestation of dialysis-related amyloidosis. *Am J Nephrol.* 1996; 16: 484-488.
21. Hakim RM, Wingard RL, Husni L, Parker RA, Parker TF 3rd. The effect of membrane biocompatibility on plasma beta 2-microglobulin levels in chronic hemodialysis patients. *J Am Soc Nephrol.* 1996; 7: 472-478.
22. Traut M, Haufe CC, Eismann U, Deppisch RM, Stein G, Wolf G. Increased binding of beta-2-microglobulin to blood cells in dialysis patients treated with high-flux dialyzers compared with low-flux membranes contributed to reduced beta-2-microglobulin concentrations. Results of a cross-over study. *Blood Purif.* 2007; 25: 432-440.
23. Koda Y, Nishi S, Miyazaki S, et al. Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. *Kidney Int.* 1997; 52: 1096-1101.
24. Copley JB, Lindberg JS. Nontransplant therapy for dialysis-related amyloidosis. *Semin Dial.* 2001; 14: 94-98.
25. Haase M, Bellomo R, Baldwin I, et al. Beta2-microglobulin removal and plasma albumin levels with high cut-offhemodialysis. *Int J Artif Organs.* 2007; 30: 385-392.
26. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi E Trapianto. *Kidney Int. 1999;* 55: 286-293.
27. Dember LM, Jaber BL. Dialysis-related amyloidosis: late finding or hidden epidemic? *Semin Dial.* 2006; 19: 105-109.
28. Penne EL, van der Weerd NC, Blankestijn PJ, et al. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. *Clin J Am Soc Nephrol*. 2010; 5: 80-86.
29. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med.* 2002; 347: 2010-2019.

30. Locatelli F, Martin-Malo A, Hannedouche T, et al. Effect of membrane permeability on survival of hemodialysis patients. *J Am Soc Nephrol.* 2009; 20: 645-654.
31. Palmer SC, Rabindranath KS, Craig JC, Roderick PJ, Locatelli F, Strippoli GF. High-flux versus low-flux membranes for end-stage kidney disease. *Cochrane Database Syst Rev.* 2012; 12: CD005016. doi: 10.1002/14651858.CD005016.pub2
32. Panichi V, Scatena A, Rosati A, et al. High-volume online haemodiafiltration improves erythropoiesis-stimulating agent (ESA) resistance in comparison with low-flux bicarbonate dialysis: results of the REDERT study. *Nephrol Dial Transplant.* 2014; 30: 682-689.
33. Jia P, Jin W, Teng J, et al. Acute Effects of Hemodiafiltration Versus Conventional Hemodialysis on Endothelial Function and Inflammation: A Randomized Crossover Study. *Medicine (Baltimore).* 2016; 95: e3440. doi: 10.1097/MD.0000000000003440.
34. Maduell F, Arias M, Durán CE, et al. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. *Nephrol Dial Transplant.* 2012; 27: 1619-1631.
35. Maduell F, Moreso F, Pons M, et al. High-efficiency post-dilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol*. 2013; 243: 487-497.
36. Maduell F, Moreso F, Mora-Macià J, et al. All-cause mortality considered by competing risks and time-dependent covariates for renal transplantation. *Nefrologia*. 2016; 36: 156-163.
37. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant*. 2013; 28: 192-202.
38. Peters SA, Bots ML, Canaud B, et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant.* 2016; 31: 978-984.
39. Davenport A, Peters SA, Bots ML, et al. Higher convection volume exchange with online hemodiafiltration is associated with survival

advantage for dialysis patients: the effect of adjustment for body size. *Kidney Int.* 2016; 89: 193-199.
40. Nubé MJ, Peters SAE, Blankestijn PJ, et al. Mortality reduction by post-dilution online-haemodiafiltration: a cause-specific analysis. HDF Pooling Project investigators: *Nephrol Dial Transplant.* 2017; 32: 548-555.
41. Gal R, Korzets A, Schwartz A, Rath-Wolfson L, Gafter U. Systemic distribution of beta 2-microglobulin-derived amyloidosis in patients who undergo long-term hemodialysis. Report of seven cases and review of the literature. *Arch Pathol Lab Med.* 1994; 118: 718-721.
42. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. *Amyloid*. 2016; 23: 209-213.
43. Uji Y, Motomiya Y, Ando Y. A circulating beta 2-microglobulin intermediate in hemodialysis patients. *Nephron Clin Pract.* 2009; 111:173-181.
44. Raj DS, Ouwendyk M, Francoeur R, Pierratos A. beta(2)-microglobulin kinetics in nocturnal haemodialysis. *Nephrol Dial Transplant.* 2000; 15: 58-64.
45. Canaud B, Assounga A, Kerr P, Aznar R, Mion C. Failure of a daily haemofiltration programme using a highly permeable membrane to return beta 2-microglobulin concentrations to normal in haemodialysis patients. *Nephrol Dial Transplant.* 1992; 7: 924-930.
46. Wong B, Collister D, Muneer M, et al. In-Center Nocturnal Hemodialysis Versus Conventional Hemodialysis: A Systematic Review of the Evidence. *Am J Kidney Dis.* 2017; 70: 218-234.
47. Campistol JM. Dialysis-related amyloidosis after renal transplantation. *Semin Dial.* 2001; 14: 99-102.
48. Tsuchida K, Takemoto Y, Nakamura T, et al. Lixelle adsorbent to remove inflammatory cytokines. *Artif Organs.* 1998; 22: 1064-1067.
49. Abe T, Uchita K, Orita H, et al. Effect of beta(2)-microglobulin adsorption column on dialysis-related amyloidosis. *Kidney Int.* 2003; 64: 1522-1528.

50. Gejyo F, Kawaguchi Y, Hara S, et al. Arresting dialysis related amyloidosis: a prospective multicenter controlled trial of direct hemoperfusion with a beta2-microglobulin adsorption column. *Artif Organs.* 2004; 28: 371-380.
51. Yamamoto Y, Hirawa N, Yamaguchi S, et al. Long-term efficacy and safety of the small-sized β2-microglobulin adsorptioncolumn for dialysis-related amyloidosis. *Ther Apher Dial.* 2011; 15: 466-474.
52. Kuragano T, Inoue T, Yoh K, et al. Effectiveness of β(2)-microglobulin adsorption column in treating dialysis-relatedamyloidosis: a multicenter study. *Blood Purif* . 2011; 32: 317-322.
53. Gejyo F, Amano I, Ando T, et al. Survey of the effects of a column for adsorption of β2-microglobulin in patients with dialysis-related amyloidosis in Japan. *Ther Apher Dial*. 2013; 17: 40-47.
54. Schindler R, Linnenweber S, Schulze M, et al. Gene expression of interleukin-1 beta during hemodialysis. *Kidney Int.* 1993; 43: 712-721.
55. Zaoui PM, Stone WJ, Hakim RM. Effects of dialysis membranes on beta 2-microglobulin production and cellular expression. *Kidney Int*. 1990; 38: 962-968.
56. Hakim RM, Wingard RL, Husni L, Parker RA, Parker TF 3rd. The effect of membrane biocompatibility on plasma beta 2-microglobulin levelsin chronic hemodialysis patients. *J Am Soc Nephrol.* 1996; 7: 472-478.
57. Haufe CC, Eismann U, Deppisch RM, Stein G. Expression of beta2-microglobulin and c-fos mRNA: is there an influence of high- or low-flux dialyzer membranes? *Kidney Int Suppl.* 2001; 78: S177-181.
58. Sonikian M, Gogusev J, Zingraff J, et al. Potential effect of metabolic acidosis on beta 2-microglobulin generation: in vivo and in vitro studies. *J Am Soc Nephrol.* 1996; 7: 350-356.
59. Baz M, Durand C, Ragon A, et al. Using ultrapure water in hemodialysis delays carpal tunnel syndrome. *Int J Artif Organs.* 1991; 14: 681-685.
60. Kleophas W, Haastert B, Backus G, Hilgers P, Westhoff A, van Endert G. Long-term experience with an ultrapure individual dialysis fluid with a batch typemachine. *Nephrol Dial Transplant.* 1998; 13: 3118-3125.

61. Susantitaphong P, Riella C, Jaber BL: Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. *Nephrol Dial Transplant.* 2013; 28: 438-446.
62. Hoshino J, Yamagata K, Nishi S, et al. Carpal tunnel surgery as proxy for dialysis-related amyloidosis: results from the Japanese society for dialysis therapy. *Am J Nephrol.* 2014; 39: 449-458.

Figure legends

Fig. 1 Comparison of CTS new incidence rates in cohorts from 1998 and 2010 in Japan. The incidence of first-time CTS surgery was significantly higher in 1998 than in the 2010 (1.77% versus 1.30%). adapted from Hoshino J, Yamagata K: Significance of the decreased risk of dialysis-related amyloidosis now proven by results from Japanese nationwide surveys in 1998 and 2010. *Nephrol Dial Transplant.* 2016; 31: 595-602 (reference 10). Used with permission of the ERA-EDTA

Fig. 2 Adjusted OR of CTS onset in the two populations in 1998 and 2010, by dialysis duration (A), age (B), pretreatment serum β2m (C) and β2m clearance (D). ORs were adjusted by dialysis duration, age, sex, primary kidney disease, modality, body mass index, albumin, CRP, Kt/V, normalized PCR and β2m clearance. In the analysis including pre-dialysis β2m, β2m removal was used instead of β2m clearance. adapted from Hoshino J, Yamagata K: Significance of the decreased risk of dialysis-related amyloidosis now proven by results from Japanese nationwide surveys in 1998 and 2010. *Nephrol Dial Transplant.* 2016; 31: 595-602 (reference 10). Used with permission of the ERA-EDTA

Fig. 3 Adjusted ORs of CTS onset. ORs were adjusted by dialysis duration, age, gender, primary kidney disease, history of smoking, history of hypertension, dialysis modality, use of high-flux membrane, BMI, serum albumin (Alb), Kt/V, nPCR, and serum β2MG clearance. CGN, chronic glomerulonephritis; DM, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; SLE, systemic lupus erythematosus. adapted from Hoshino J, Yamagata K: Carpal tunnel

surgery as proxy for dialysis-related amyloidosis: results from the Japanese Society for Dialysis Therapy. *Am J Nephrol*. 2014; 39: 449-458 (reference 62). Used with permission of S. Karger AG

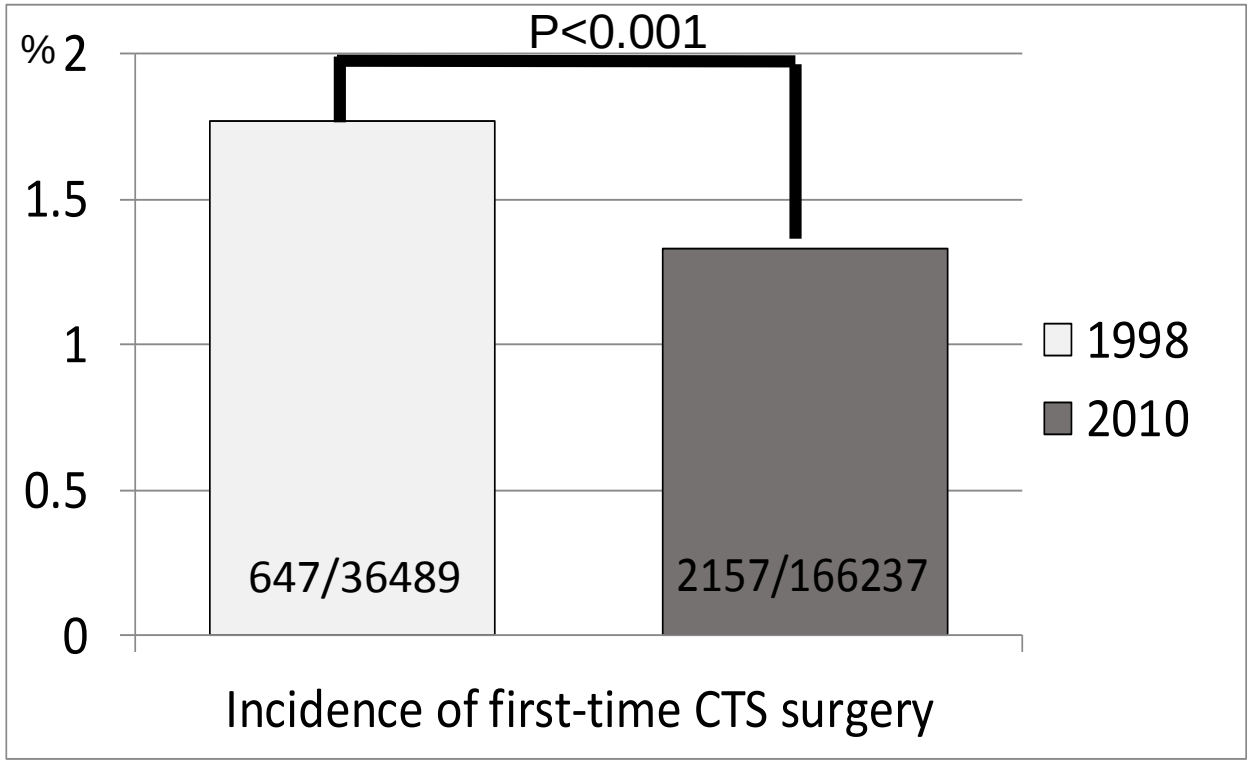
P<0.001
% 2
1.5
1
0.5
0
647/36489
2157/166237
1998
2010
Incidence of first-time CTS surgery

FIGURE 1

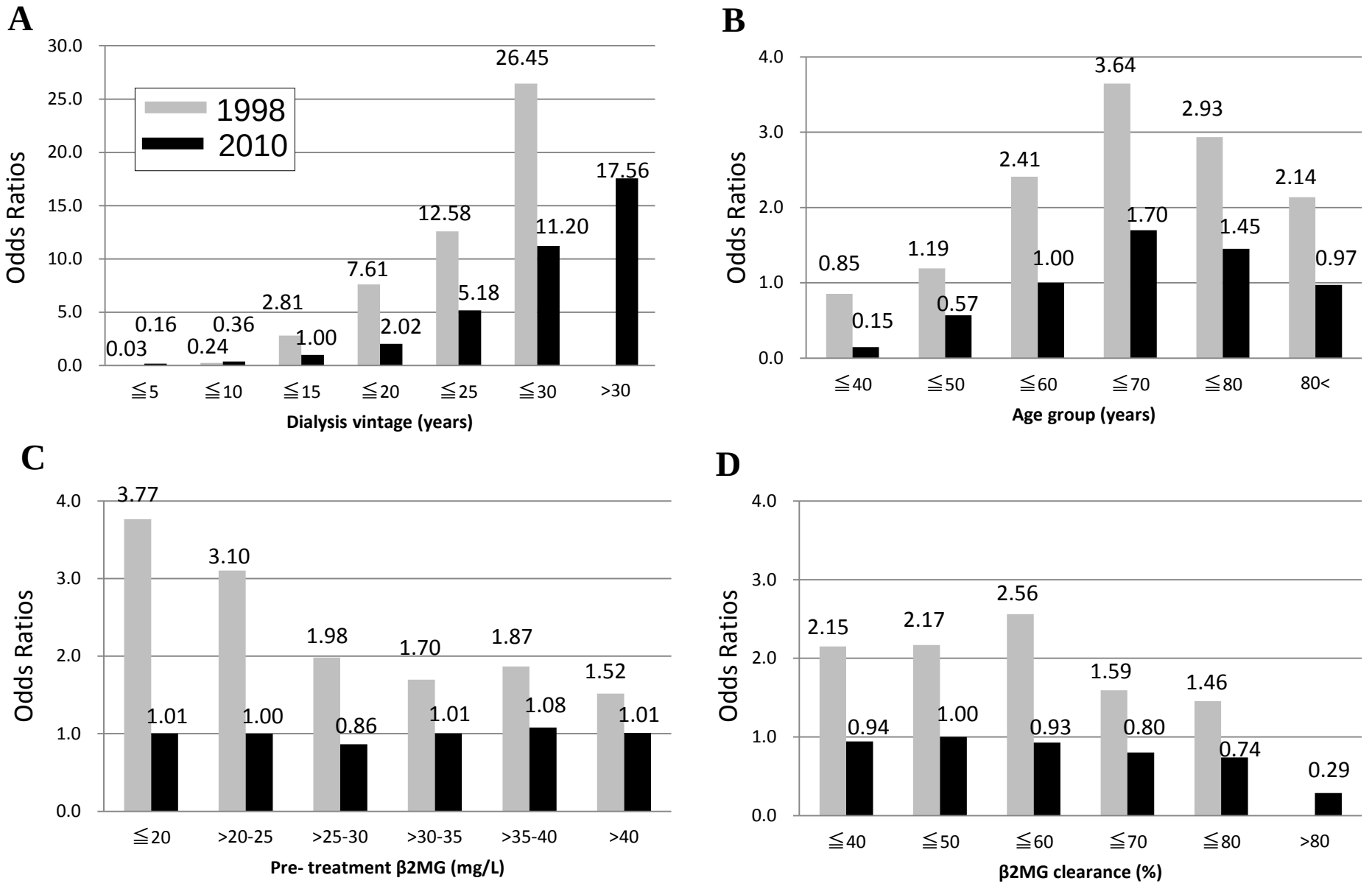
A
Odds Ratios
30.0
25.0
20.0
15.0
10.0
5.0
0.0
1998
2010
0.03
0.16
0.24
0.36
2.81
1.00
7.61
2.02
12.58
5.18
26.45
11.20
17.56
≦5
≦10
≦15
≦20
≦25
≦30
>30
Dialysis vintage (years)
B
Odds Ratios
4.0
3.0
2.0
1.0
0.0
0.85
0.15
1.19
0.57
2.41
1.00
3.64
1.70
2.93
1.45
2.14
0.97
≦40
≦50
≦60
≦70
≦80
80<
Age group (years)
C
Odds Ratios
4.0
3.0
2.0
1.0
0.0
3.77
1.01
3.10
1.00
1.98
0.86
1.70
1.01
1.87
1.08
1.52
1.01
≦20
>20-25
>25-30
>30-35
>35-40
>40
Pre- treatment β2MG (mg/L)
D
Odds Ratios
4.0
3.0
2.0
1.0
0.0
2.15
0.94
2.17
1.00
2.56
0.93
1.59
0.80
1.46
0.74
0.29
≦40
≦50
≦60
≦70
≦80
>80
β2MG clearance (%)

FIGURE 2

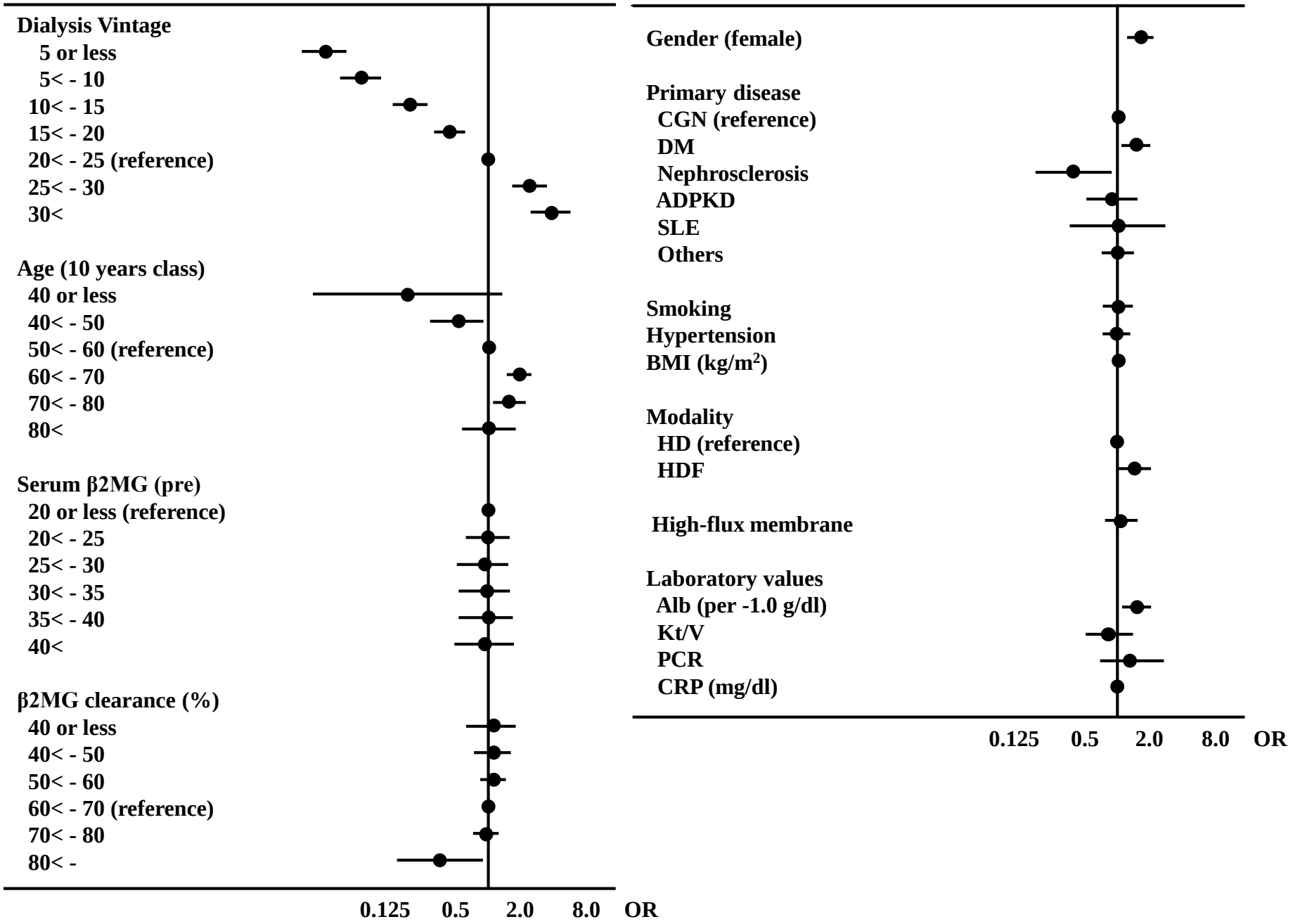
Dialysis Vintage
5 or less
5< - 10
10< - 15
15< - 20
20< - 25 (reference)
25< - 30
30<
Age (10 years class)
40 or less
40< - 50
50< - 60 (reference)
60< - 70
70< - 80
80<
Serum β2MG (pre)
20 or less (reference)
20< - 25
25< - 30
30< - 35
35< - 40
40<
β2MG clearance (%)
40 or less
40< - 50
50< - 60
60< - 70 (reference)
70< - 80
80< -
0.125
0.5
2.0
8.0
OR
Gender (female)
Primary disease
CGN (reference)
DM
Nephrosclerosis
ADPKD
SLE
Others
Smoking
Hypertension
BMI (kg/m2)
Modality
HD (reference)
HDF
High-flux membrane
Laboratory values
Alb (per -1.0 g/dl)
Kt/V
PCR
CRP (mg/dl)
0.125
0.5
2.0
8.0
OR

FIGURE 3