Beta-2 microglobulin and all-cause mortality in the era of high-flux hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study

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ABSTRACT

Background. Beta-2 microglobulin (β2M) accumulates in hemodialysis (HD) patients, but its consequences are controversial, particularly in the current era of high-flux dialyzers. High-flux HD treatment improves β2M removal, yet β2M and other middle molecules may still contribute to adverse events. We investigated patient factors associated with serum β2M, evaluated trends in β2M levels and in hospitalizations due to dialysis-related amyloidosis (DRA), and estimated the effect of β2M on mortality.

Methods. We studied European and Japanese participants in the Dialysis Outcomes and Practice Patterns Study. Analysis of DRA-related hospitalizations spanned 1998–2018 (n = 23 976), and analysis of β2M and mortality in centers routinely measuring β2M spanned 2011–18 (n = 5332). We evaluated time trends with linear and Poisson regression and mortality with Cox regression.

Results. Median β2M changed nonsignificantly from 2.71 to 2.65 mg/dL during 2011–18 (P = 0.87). Highest β2M tertile patients (>2.9 mg/dL) had longer dialysis vintage, higher C-reactive protein and lower urine volume than lowest tertile patients (<2.3 mg/dL). DRA-related hospitalization rates [95% confidence interval (CI)] decreased from 1998 to 2018 from 3.10 (2.55–3.76) to 0.23 (0.13–0.42) per 100 patient-years. Compared with the lowest β2M tertile, adjusted mortality hazard ratios (95% CI) were 1.16 (0.94–1.43) and 1.38 (1.13–1.69) for the middle and highest tertiles. Mortality risk increased monotonically with β2M modeled continuously, with no indication of a threshold.

Conclusions. DRA-related hospitalizations decreased over 10-fold from 1998 to 2018. Serum β2M remains positively associated with mortality, even in the current high-flux HD era.

Keywords: β2M, dialysis, high flux dialysis, dialysis-related amyloidosis, ESRD
INTRODUCTION

Beta-2 microglobulin (ß2M) is a protein expressed on the surfaces of all nucleated cells; it is a middle molecule (molecular weight, 11.8 kDa) and a light-chain component of the major histocompatibility Class I molecules associated with the heavy-chain components on cell surfaces. Excess ß2M forms fibrillar structures and amyloid deposits [1], primarily in osteoarticular structures and the viscera [2, 3]. ß2M accumulation in the blood has been associated with a decrease in residual kidney function [4–6] and an increased risk of all-cause, cardiovascular and infectious deaths [7–11].

ß2M clearance has long been a surrogate for middle-molecule clearance among patients receiving hemodialysis (HD) [12]. The combination of declining residual kidney function and a low rate of ß2M removal by low-flux cuprophane and cellulose acetate dialysis membranes did not provide sufficient ß2M reduction [13]. This impaired ß2M clearance became associated with a higher risk of dialysis-related amyloidosis (DRA), a rare but devastating complication resulting in carpal tunnel syndrome (CTS), organ deposition of amyloid deposits, and a painful and debilitating arthropathy. In addition to the DRA-related increased hospitalization rates and quality of life issues observed during the utilization period of these membranes, ß2M accumulation potentially contributed to morbidity and mortality from other causes.

In contrast, modern HD therapy includes the use of highly permeable and high-flux membranes that enhance ß2M clearance. Yet dialysis treatment itself may increase ß2M production by acting as an inflammatory stimulus; this may vary by membrane type and dialysate buffer (acetate versus bicarbonate) and the use of ultrapure dialysate [2, 14]. The combined use of ultrapure dialysates and advanced biocompatible membranes is thought to help reduce inflammation and ß2M production [15, 16].

Although the incidence of DRA has decreased over time [17], the resulting impact of increasing ß2M removal remains controversial. The Hemodialysis (HEMO) study did not show a beneficial effect of ß2M removal on mortality at many HD centers. For analysis of DRA in Phases 1–6, we restricted to sites that routinely measured ß2M; this was defined as ≥50% of patients having ß2M levels reported in ≥50% of their 4-month follow-up visit intervals.

A central Institutional Review Board approved each study phase. We obtained additional study approvals and informed patient consents as required by national and local ethics regulations.

Statistical analyses

For ß2M analyses, we ascertained baseline patient characteristics as of the date of ß2M measurement. We employed linear regression to evaluate a time trend in ß2M levels across DOPPS Phases 4–6, adjusting for age, sex, dialysis vintage, diabetes diagnosis and region (Japan or Europe). We chose generalized estimating equations (GEEs) with exchangeable working correlation structure to account for patients clustered in facilities. Assessment of DRA-related hospitalization rates across DOPPS Phases 1–6 was achieved with Poisson regression, both unadjusted and adjusted as in the linear model above, and using GEE with independent working correlation structure. We defined DRA-related hospitalizations as those where the identified cause was listed as DRA or CTS.

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33rd, 67th and 90th percentiles; adjustments were as in the model with categorical $\beta_2$M. Patient clustering within facilities was accounted for with the robust sandwich covariance estimator [24]. Time at risk for all Cox models began at baseline and ended at death or last date of study follow-up.

We used multiple imputations, implemented by IVEware [25], to impute missing covariate values for the survival analyses. Overall, missingness was low, at <2% for all covariates except for $K_t/V_{urea}$ (11%) and residual urine volume (12%). We imputed 20 complete data sets, performed all Cox regressions with each data set and combined the results using Rubin’s rules [26]. All analyses used SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

In a cross-sectional, unadjusted analysis, patients in the highest $\beta_2$M tertile (>2.9 mg/dL) had longer dialysis vintage, greater likelihood of urine volume >200 mL/day, lower prevalence of diabetes, and higher levels of serum creatinine, phosphorus and C-reactive protein (CRP) than patients in the middle (2.3–2.9 mg/dL) and lowest (<2.3 mg/dL) $\beta_2$M tertiles (Table 1). We observed little association between $\beta_2$M and HD treatment time or catheter use. Among patients using HDF, patients in the highest $\beta_2$M tertile tended to have lower replacement fluid volume than patients in the middle and lowest tertiles.

Across DOPPS Phases 4–6 (2011–18), median (IQR) $\beta_2$M changed nonsignificantly from 2.71 mg/dL (2.28–3.14) to 2.67 (2.22–3.12) to 2.65 (2.28–3.05). In adjusted regression, the P-value for linear trend in $\beta_2$M levels over DOPPS Phases was $P = 0.87$. The crude rate of DRA-related hospitalizations fell sharply across Phases 1–6 (1998–2018), from 3.10 (95% CI 2.55–3.76) to 0.23 (95% CI 0.13–0.42) hospitalizations per 100 patient-years (Supplementary data, Figure S1). Consistent with the crude rates, the adjusted rate of hospitalizations declined across phases ($P < 0.0001$).

Median (IQR) follow-up time for mortality analyses was 2.2 years (1.5–2.8) in Japan and 1.3 years (0.8–2.1) in Europe. Crude death rates in the lowest, middle and highest $\beta_2$M tertiles were 4.5, 4.9 and 6.0 deaths per 100 patient-years in Japan and 11.1, 15.1 and 14.9 in Europe. In adjusted Cox regression with data combined across regions, the highest $\beta_2$M tertile was strongly associated with increased risk of death (HR = 1.38, 95% CI 1.13–1.69) relative to the lowest tertile (Table 2). This finding was replicated within all subgroups. Among patients with urine volume >200 mL/day, the associations were notably stronger, with both the highest (HR = 1.96, 95% CI 1.34–2.86) and middle (HR = 1.56, 95% CI 1.04–2.32) tertiles having increased risk of death relative to the lowest. With $\beta_2$M coded as a spline (Figure 2), the adjusted hazard of death increased monotonically across the range of $\beta_2$M values. These findings were nearly identical in separate models that additionally adjusted for the dialysis treatment characteristics of $K_t/V_{urea}$, treatment time and use of HDF versus HD (Supplementary data, Table S1).

DISCUSSION

In this study, despite the observation of non-significant changes in circulating $\beta_2$M during DOPPS Phases 4–6 (2011–18), the rate of DRA-related hospitalizations decreased 10-fold across Japan and Europe from 1998 to 2018. Higher serum $\beta_2$M levels were associated with lower survival rates in both Japan and Europe in...
### Table 1. Patient characteristics according to 2M tertile, by region

| Characteristics          | Europe Lowest (n = 591) | Europe Middle (n = 374) | Europe Highest (n = 528) | Japan Lowest (n = 1214) | Japan Middle (n = 1426) | Japan Highest (n = 1199) |
|--------------------------|-------------------------|-------------------------|--------------------------|-------------------------|-------------------------|--------------------------|
| Male, %                  | 65                      | 59                      | 62                       | 67                      | 67                      | 63                       |
| Age, years               | 67 ± 15                 | 69 ± 15                 | 66 ± 15                  | 66 ± 12                 | 65 ± 12                 | 65 ± 12                  |
| Body mass index, kg/m²   | 26 ± 5                  | 26 ± 5                  | 25 ± 5                   | 22 ± 4                  | 22 ± 3                  | 21 ± 4                   |
| Pain (self-report, higher is less pain) | 61 ± 32                | 50 ± 32                 | 55 ± 31                  | 70 ± 30                 | 67 ± 29                 | 65 ± 31                  |
| Urine volume <200 mL/day | 54                      | 73                      | 80                       | 61                      | 80                      | 89                       |
| Treatment characteristics |                         |                         |                          |                         |                         |                          |
| Kt/V measured            | 1.6 ± 0.3               | 1.6 ± 0.3               | 1.6 ± 0.3                | 1.3 ± 0.3               | 1.4 ± 0.3               | 1.5 ± 0.3                |
| Treatment time, h        | 3.9 ± 0.4               | 3.9 ± 0.6               | 3.9 ± 0.4                | 3.8 ± 0.5               | 4.0 ± 0.5               | 4.1 ± 0.4                |
| HDF, %                   | 26                      | 32                      | 20                       | 7                       | 13                      | 15                       |
| Catheter use, %          | 33                      | 26                      | 32                       | 1                       | 1                       | 0                        |
| HDF replacement fluid volume, % |                         |                         |                          |                         |                         |                          |
| <4.0 L                   | 0                       | 0                       | 0                        | 6                       | 3                       | 3                        |
| 4.0–15.0 L               | 10                      | 5                       | 7                        | 33                      | 37                      | 43                       |
| 15.1–20.0 L              | 26                      | 30                      | 41                       | 3                       | 1                       | 2                        |
| >20.0 L                  | 64                      | 65                      | 51                       | 59                      | 59                      | 51                       |
| Laboratory data          |                         |                         |                          |                         |                         |                          |
| 2M, mg/dL                | 1.7 ± 0.4               | 2.6 ± 0.2               | 3.8 ± 0.9                | 1.9 ± 0.3               | 2.6 ± 0.2               | 3.4 ± 0.5                |
| Albumin, g/dL            | 3.8 ± 0.5               | 3.8 ± 0.5               | 3.8 ± 0.5                | 3.6 ± 0.4               | 3.7 ± 0.4               | 3.6 ± 0.4                |
| Creatinine, mg/dL        | 6.9 ± 2.4               | 8.2 ± 2.4               | 9.0 ± 2.5                | 8.5 ± 2.6               | 10.8 ± 2.7              | 11.1 ± 2.6               |
| Phosphorus, g/dL         | 4.3 ± 1.2               | 4.5 ± 1.4               | 4.7 ± 1.5                | 5.1 ± 1.2               | 5.3 ± 1.4               | 5.5 ± 1.5                |
| Parathyroid hormone, pg/mL | 304 ± 286              | 333 ± 330              | 324 ± 337               | 180 ± 189              | 164 ± 167              | 163 ± 148               |
| TSAT, %                  | 26.4 ± 12.0             | 26.6 ± 12.1             | 27.0 ± 12.7             | 24.5 ± 11.6             | 25.2 ± 12.2             | 23.6 ± 12.5             |
| Ferritin, ng/mL          | 420 ± 399               | 429 ± 307              | 495 ± 436              | 135 ± 193              | 143 ± 232              | 152 ± 271               |
| Hemoglobin, g/dL         | 11.5 ± 1.5              | 11.6 ± 1.5              | 11.6 ± 1.5              | 10.7 ± 1.2              | 10.6 ± 1.3              | 10.7 ± 1.3              |
| CRP, mg/L                | 13.0 ± 32.2             | 10.9 ± 16.8             | 16.2 ± 27.9             | 3.8 ± 14.3             | 4.0 ± 10.6             | 7.5 ± 19.0              |
| Comorbidities, %         |                         |                         |                          |                         |                         |                          |
| Diabetes                 | 45                      | 32                      | 28                       | 49                      | 39                      | 36                       |
| Hypertension             | 93                      | 86                      | 83                       | 83                      | 85                      | 81                       |
| Coronary heart disease   | 32                      | 27                      | 29                       | 27                      | 28                      | 27                       |
| Cerebrovascular disease  | 14                      | 17                      | 15                       | 13                      | 17                      | 15                       |
| Congestive heart failure | 21                      | 23                      | 23                       | 17                      | 19                      | 21                       |
| Peripheral vascular disease | 36                    | 37                      | 33                       | 14                      | 15                      | 16                       |
| Other cardiovascular disease | 32                    | 35                      | 31                       | 20                      | 26                      | 28                       |
| Cancer (nonskin)         | 12                      | 17                      | 16                       | 12                      | 11                      | 12                       |
| GI bleeding              | 5                       | 5                       | 2                        | 3                       | 4                       | 4                        |
| Lung disease             | 20                      | 21                      | 16                       | 4                       | 4                       | 5                        |
| Neurologic disease       | 14                      | 14                      | 13                       | 7                       | 8                       | 6                        |
| Psychiatric disorder     | 18                      | 18                      | 23                       | 4                       | 5                       | 4                        |
| Recurrent cellulitis or gangrene | 8                   | 6                       | 9                        | 3                       | 2                       | 4                        |
| Carpal tunnel            | 2                       | 3                       | 3                        | 5                       | 5                       | 4                        |

2M tertiles are (≤2.3 mg/dL), middle (2.3–2.9) and highest (>2.9). Characteristics are reported as mean ± SD or %.

*aSelf-reported pain score from the Kidney Disease Quality of Life-36 Survey (KDQOL-36). Note that 44% of patients had missing data for this item.

Analysis of data from the current high-flux dialysis era (2011–18), even with adjustment for numerous patient and dialysis treatment characteristics.

A subanalysis of the HEMO study showed that 2M levels >3.5 mg/dL were associated with a higher risk of death than 2M levels <2.75 mg/dL. The Japanese Society for Dialysis Therapy (JSCT) clinical guideline for maintenance HD showed that 2M levels ≥3.0 mg/dL were associated with a higher risk than 2M levels between 2.5 and 3.0 mg/dL. Based on this finding, the JSCT clinical guideline for maintenance HD recommended achieving serum 2M levels <3.0 mg/dL. However, in our study, the relationship between mortality and 2M levels was monotonic, without a clear indication of a threshold in the range of 2M from 1.4 to 4.0 mg/dL. Considering these findings, targeting still lower 2M levels may improve patients’ prognosis. However, the causality of this association cannot be assessed by the present observational study. Interventional studies are needed to show the threshold of 2M levels for better survival.

The results of our study corroborate the importance of middle molecules, including serum 2M accumulation as a marker for death. Thus, appropriate selection of dialyzer membrane material is important for the effective clearance of 2M and other middle molecules, with potential implications for patient prognosis. Indeed, high-flux membrane dialysis effectively removes 2M and is recommended by the JSCT clinical guideline for maintenance HD, the European Best Practice Guideline on dialysis strategies and the Kidney Health.
Table 2: HRs (95% CI) for all-cause mortality by β2M tertile, relative to the lowest tertile

| Patient group | n  | Deaths | Lowest (95% CI) | Middle (95% CI) | Highest (95% CI) | Interaction P-value |
|---------------|----|--------|----------------|----------------|----------------|-------------------|
| All patients  | 5332 | 696    | 1 (ref)        | 1.16 (0.94–1.43) | 1.38 (1.13–1.69) |                   |
| By region     |     |        |                |                |                |                   |
| Europe        | 1493 | 288    | 1 (ref)        | 1.32 (1.00–1.74) | 1.44 (1.09–1.91) | 0.40              |
| Japan         | 3839 | 408    | 1 (ref)        | 1.11 (0.62–1.50) | 1.32 (1.00–1.75) |                   |
| By residual urine volume |     |        |                |                |                |                   |
| ≥200 mL/day   | 1367 | 139    | 1 (ref)        | 1.56 (1.04–2.32) | 1.96 (1.34–2.86) | 0.02              |
| <200 mL/day   | 3965 | 557    | 1 (ref)        | 1.09 (0.86–1.40) | 1.28 (1.01–1.62) |                   |
| By dialysis modality |     |        |                |                |                |                   |
| HDF           | 823  | 112    | 1 (ref)        | 1.04 (0.69–1.56) | 1.30 (0.79–2.15) | 0.65              |
| HD            | 4509 | 584    | 1 (ref)        | 1.17 (0.93–1.48) | 1.40 (1.12–1.73) |                   |

Based on Cox regression, adjusting for age, sex, region (Europe or Japan), DOPPS phase, dialysis vintage, residual urine volume (≥200 or <200 mL/day), serum albumin and five comorbidities (diabetes, coronary heart disease, congestive heart failure, cerebrovascular disease and other cardiovascular diseases). Interaction P-values test the interactions between β2M and each of region, residual urine volume and dialysis modality (HDF or HD). β2M tertiles are lowest (<2.3 mg/dL), middle (2.3–2.9) and highest (>2.9).

FIGURE 2: Adjusted HRs (95% CI) for all-cause mortality by continuous β2M level, relative to a β2M of 2.3 mg/dL.

Based on Cox regression, with β2M coded as a natural cubic spline with knots at 1.7, 2.3, 2.9 and 3.5 mg/dL, corresponding to the 10th, 33rd, 67th and 90th percentiles of β2M in our sample. Adjusted for age, sex, region (Europe or Japan), DOPPS Phase, dialysis vintage, residual urine volume (≥200 or <200 mL/day), serum albumin and five comorbidities (diabetes, coronary heart disease, congestive heart failure, cerebrovascular disease and other cardiovascular diseases). Plot extends between the 5th and 95th percentiles of β2M, that is, between 1.4 and 4.0 mg/dL.

Australia-Caring for Australasians with Renal Impairment Guideline Dialysis adequacy [11, 29, 30].

In our subgroup analyses, the mortality risk associated with elevated β2M was greater for patients with residual urine volume ≥200 versus <200 mL/day (P = 0.02 for interaction). While preserving residual kidney function is an important strategy to maintain low β2M levels, the cause of this stronger positive association of mortality with β2M among persons with residual urine volume requires further study. Perhaps not all urine volume represents the same degree of clearance, and higher levels of β2M may serve as a surrogate for impaired renal clearance of other middle and large molecules. In this regard, Evenepoel et al. [31] demonstrated that in a cohort of HD patients, 17% of total β2M clearance was due to residual urinary clearance compared with only 6% of total urea clearance, suggesting that residual kidney clearance of β2M is significant even among HD patients. The presence of a higher inflammatory burden may also play a role among patients with residual kidney function, as CRP levels are higher in patients with higher β2M levels. In another subgroup analysis, the risk of death in patients with high versus low β2M was similar in HD and HDF, indicating that the negative impact of high β2M levels on patient outcome can be observed across modalities. Further study is needed to quantify the relative contribution of β2M production versus excretion on the excess mortality risk of β2M among patients with residual kidney function.

A meta-analysis showed that convective therapies (high-flux HD, hemofiltration or HDF) are more effective than low-flux HD in reducing all-cause mortality; increasing the clearance of middle molecules (β2M); reducing the circulating levels of homocysteine, advanced glycation end products and pentosidine; and decreasing serum concentration of inflammatory biomarkers [32]. Furthermore, medium cut-off dialyzers hold the potential to positively impact β2M levels, since these novel filters remove a wide range of middle and larger molecules more effectively than high-flux HD [33]. Although a higher residual kidney function, higher dialyzer flow, higher cut-off membranes and convective therapies may reduce serum β2M level, none appears individually sufficient to normalize β2M levels in many patients. Further studies are necessary to explore whether or not enhanced removal of β2M via dialytic approaches stands to improve survival for HD patients, which could not be assessed in the present study.

The frequency of serum β2M measurements was higher in Japan than in the included European countries and much higher than in other DOPPS countries. Since the JSDT clinical guideline recommends routine measurement of serum β2M level every 3 months, it is common practice in Japan to select an appropriate dialyzer with high-flux membrane characteristics and change to other modes of dialysis therapy such as HDF in patients with high serum β2M levels [11]. The impact of the practice of using β2M levels to guide clinicians in the selection of dialyzer and dialysis modality on clinical outcomes deserves further investigation.

This work has some limitations largely related to the observational nature of this study, which cannot definitively establish a causal relationship between β2M and mortality. In this regard, unmeasured confounders may bias the results. The positive association between β2M levels and mortality may possibly reflect patient factors that lead to higher...
CONCLUSIONS

The current era of high-flux HD provides the technological means to support improved clearance of β2M and other middle molecules. Despite this treatment availability, some HD patients still experience higher levels of serum β2M, a status we found to be associated with increased mortality, even when controlling for potential confounders. The dialysis community needs future studies to evaluate the effectiveness of evolving dialytic strategies that target yet greater clearance of β2M and other middle or large molecules and their impact on clinical outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

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