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Beta-2-Microglobulin Level Increases with Advanced CKD Stages: The Implications and Significance

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1. Abstract

1.1. Introduction: Beta2-microglobulin (β-2M) production is constant among healthy population, making it appropriate proxy for the estimated Glomerular-Filtration-Rate (eGFR).

1.2. Methodology: This clinical observational study was conducted at the Royal Hospital, Muscat. It aims to define the level of serum-β-2M along with their clinical and investigatory profiles. Data collected prospectively via electronic system.

1.3. Results: 866 had Chronic-Kidney-Disease (CKD), of which 476 (55%) were males.

A total of 552 had stage-1CKD with β-2M (mg/dl) levels found to be 3.04(5) in 287 male patients and 2.68(3.9) in 265 females. Stage-2 CKD, a total of 121 patients with 69 males and 52 females had β-2M levels 4.15 (2.9) and 4.06 (3.3) respectively. A total of 91 patients with Stage-3CKD, of which 61 were males and 30 were females, with β-2M levels being 7.14 (5.3) and 8.96 (7.2) respectively.

1.4. Conclusions: Kidney-function is the main determinant of serum β-2M by affecting both filtration via glomeruli of the kidney and the generation of β-2M. Uremic solutes that are retained in kidney failure institutes a key cause for the sharp increase of β-2M in CKD. Management strategies for various hematological disorders, in particular during chemotherapy, need to take into consideration maintenance of a good kidney-function especially improvement of hydration and the acid-base control.

2. Key words: Beta2-Microglobulin (β-2M); estimated Glomerular-Filtration-Rate (eGFR); Chronic-Kidney-Disease (CKD); Uremic solutes; Multiple Myeloma; Hodgkin's lymphoma; Non-Hodgkin's Lymphoma; Solid Tumors

3. Introduction

The β-2 microglobulin (β-2M) is a low molecular weight, 11,800 Da, size 11 Å, protein, which is, associated with both classical and non-classical major histocompatibility MHC-Class I molecules [1-4]. Approximately 30% of these proteins are associated with the polypeptide chain of Class I HLA antigens and are present on the surface of all nucleated cells including lymphocytes and macrophages and are critical for antigen presentation. The protein has a tertiary structure and is thus similar to the constant domain of the immunoglobulin molecules [1-4].

β-2M is freely filtered by the kidney glomeruli, and almost all of it, 99.9%, is reabsorbed and metabolized in the proximal tubule [5,6]. Beta2 microglobulin production is constant among healthy population, thus making it appropriate as a proxy for the estimated Glomerular Filtration Rate (eGFR) and therefore is predominantly a biomarker of filtration. β-2M can become a novel glomerular filtration marker that has stronger associations with adverse outcomes than creatinine [5].

Serum β-2M concentrations are impacted by the amount generated and shed by various nucleated cells, kinetic mechanisms, body distribution and the percentage of quantity removed through kidney filtration by glomeruli and kidney metabolism by various tubules [5,7]. In normal situations, the turnover of various nucleated cells results in the production of 132m into the plasma and this is then excreted by normally functioning kidneys at a rate of 150 to 200 mg/day, resulting in a steady-state plasma level of approximately 1 to 2 mg/L [5]. In patients with no residual renal function, plasma levels reach up to approximately 50 mg/L [8,9]. However, β-2M serum levels are elevated in many inflammatory conditions associated with several medical conditions [10-13].

In recent years, the pattern of effectiveness of serum β-2M concentrations in monitoring various diseases has been constantly emphasized by various studies [14-18]. The increased concentration of the protein is found chiefly in patients suffering from lymphoproliferative diseases, Chronic Kidney Disease (CKD) including end stage (ESKD), diabetic kidney disease and autoimmune diseases including Systemic Lupus Erythematous (SLE) and Rheumatoid Arthritis (RA). As a result of T and B cells activation, β-2M is released, resulting in the elevation of its serum concentration level [14-18]. Also, there is an increasing of chronic kidney disease (CKD) across the world of both incidence and prevalence with various comorbidities [19-23].

3.1. Objectives:

To define the level of serum β-2M along with their clinical and investigatory profiles of patients that had Beta2 microglobulin test. β-2M is only performed at the central lab of MOH situated at the Royal Hospital and hence it covers the entire country.

We aim to evaluate the following:

A. **General β-2M with**
a. Clinical presentation
b. Distribution of disease and which organs were involved
c. Laboratory tests and correlation to clinical presentation

B. **β-2M in relation with**
a. Gender
b. End-stage kidney disease status
c. Comorbidities such as Diabetes, Hypertension, Chronic kidney disease, Autoimmune disorders and Malignancy
d. Infectious status

3.2. Methodology:

This is an observational clinical study conducted at the Royal Hospital, which has an excellent medical record and IT system, where everything is computerized; called Al Shifa system, which has received international certification for excellence in its achievement. All data is collected prospectively by this electronic system. A list of all patients that have been tested for serum β-2M were provided by the electronic medical system, including those who had kidney dysfunction in a hard copy data sheet.

3.3. Inclusion and Exclusion criteria:

This data was downloaded into to an excel sheet and examined by the researchers, ensuring every data point is correct with all the required values for each patient, which was then rechecked by other team members periodically. Once all the data was entered, it was analyzed using STATA software.

All researchers were involved in the quality control of data and the main investigator, alongside an epidemiologist, was the head of the team to ensure the quality based on the institution standard of data control and to maintain the highest standard. Patients were given study numbers and so only the principal investigator will have access to the identity of the patients and the database was password protected to maintain patient confidentiality.

Data were analyzed using the STATA statistical software package, version 13.1 (StataCorp LP, College Station, Texas). Data were described as frequencies and percentages for categorical variables. Continuous variables were reported as median and ranges or as mean and Standard Deviations (SDs). Age data are presented as mean ± SD (SD or 95% CI).

4. Results

A total of 901 patients' data was collected from the Royal Hospital during the period of 2006 to 2017 through the computerized information medical system. Male constituted 54.8% and 45.2% were female patients. The mean age for males was 45.92 years and for females was 44.62 years. Their mean BMI was 24.9 and 25.6 respectively, out of which, 31.6% patients were residing in Muscat and the other 68.4% were from outside of Muscat.

As shown in Table 1, the patients were included from various departments including Nephrology, Oncology, Hematology, Radiotherapy and others such as acute medicine, urology, neurology and paediatrics. In Nephrology department, a total of 55 patients were tested for serum Beta2 microglobulin levels out of which 32 (58%) were males and 23 (48%) were females, whereas in Hemato-oncolgy department total of 692 patients consisting of 387 (60%) males and 305 (40%) females were tested. The Department of Radiotherapy tested 34 patients while in other departments a total of 120 patients were tested of which 54 (45%) males and 66 (55%) females.

Table 1: Shows the distribution of Patient by gender for different departments.

Departments	Male	Female	Total	Values	
				Chi2	Pr
Hematology	175	106	281	13.63	0.09
Oncology	212	199	411		
Nephrology	32	23	55		
Radiotherapy	21	13	34		
Others	54 (45%)	66 (55%)	120		
Departments					
Nephrology	32 (58%)	23 (48%)	55	0.15	0.69
Others	462	384	846		
Departments					
Hematoncology	387 (60%)	305 (40%)	692	1.44	0.22
Others	107	102	209		

From Table 2, it is evident that patients had various diagnosis ranging from Multiple Myeloma, Hodgkin's lymphoma, Non-Hodgkin's Lymphoma, Solid Tumors such as Colon cancer, Breast cancer, sarcoma, germ cell tumor, hepatic carcinoma, lung cancer and others including Chronic Kidney disease, End stage renal disease, Anemia, Ulcerative colitis, Connective tissue disorders and infective illness. Those who were diagnosed with Multiple Myeloma were a total of 192 patients of which 119 (62%) were males and 73 (38%) were females. Those patients with Lymphoma, including both Hodgkin's and Non-Hodgkin's, were a total of 400 consisting of 204 (51%) males and 196 (49%) females. Those with solid tumors were 65 (59%) males and 46 (41%) females coming to a total of 111 patients and others included a total of 198 patients consisting of 106 (54%) males and 92 (46%) females.

Table 2: Shows the distribution of patient by gender according to various different diagnosis.

Diagnosis	Male	Female	Total	Values	
				Chi2	Pr
Multiple myeloma	119	73	192	7.82	0.09
Hodgkin's lymphoma	120	107	227		
Non-Hodgkin's lymphoma	84	89	173		
Solid tumors	65 (59%)	46 (41%)	111		
Others	106 (54%)	92 (46%)	198		
Diagnosis					
Blood disorders	323	269	592	0.77	0.67
Solid tumors	65	46	111		
Others	106	92	198		
Diagnosis					
Myleoma	119 (62%)	73 (38%)	192	5.02	0.02
Others	375	334	709		
Diagnosis					
Lymphoma	204 (51%)	196 (49%)	400	4.25	0.03
Others	290	211	501		

In Table 3, comorbidities in male and female patients were analyzed that shows the following. Diabetes was seen in 164 (33.2%) males and 141 (34.6%) females whereas Hypertension was diagnosed in 234 (47.4%) males and 159 (39.1%) females. Males with Dyslipidemia were 18.2% and obesity were 17.2% while females had 22.1% of them with Dyslipidemia and 25.3% with obesity. Autoimmune disorders were seen 4.5% in males and 4.4% in females of which, ANA was positive in 2% males and 3.4% females, Anti-ds DNA was positive in 0.2% males and 0.5% females, Rheumatoid factor present in 0.8% males and 0.7% females and ENA positive in 0.2% males and 1.2% females.

Patients with hematological malignancies were identified in 308 (62.3%) males and in 238 (58.5%) females while non-hematological malignancies were diagnosed in 84 (17%) males and 75 (18.4 %) females. Chronic infections such as HIV, Hepatitis B and C were tested positive in some patients. In males, HIV was seen in 1%, Hepatitis B in 13% and Hepatitis C in 2% while in females it was 0.7%, 11.8% and 1.5% respectively. Patients having End-stage kidney disease on renal replacement therapy accounted for 13 (2.6%) in males and 4 (1%) in females while 13.2% male patients and 18.4% female patients both had tested positive for presence of white blood cell and red blood cells in urine.

Table 3: Shows the distribution of patient by gender across several comorbidities and laboratory investigations.

Co-morbidities	Male (494)		Female (407)		Values		Male Yes%	Female Yes%
	Yes	No	Yes	No	Chi2	Pr		
Diabetes mellitus	164	330	141	266	0.2	0.64	33.2	34.6
Hypertension	234	260	159	248	6.25	0.01	47.4	39.1
Dyslipidemia	90	404	90	317	2.11	0.14	18.2	22.1
Obesity	85	409	103	304	8.86	0	17.2	25.3
Autoimmune disorders	22	472	18	389	0	0.98	4.5	4.4
ANA	10	92	14	83	1	0.31	2	3.4
Anti ds DNA	1	92	2	93	0.31	0.57	0.2	0.5
Rheumatoid factor	4	54	3	67	0.41	0.51	0.8	0.7
ENA	1	47	7	41	0.9	0.02	0.2	1.7
Hematological malignancy	308	186	238	169	1.4	0.23	62.3	58.5
Non-hematological malignancy	84	410	75	332	0.31	0.57	17	18.4
Chronic HIV	5	488	3	403	0.19	0.66	1	0.7
Chronic Hepatitis B	64	429	48	358	0.27	0.6	13	11.8
Chronic Hepatitis C	10	483	6	400	0.38	0.53	2	1.5
Urine WBC	65	428	75	328	4.95	0.02	13.2	18.4
Urine RBC	65	428	75	328	4.95	0.02	13.2	18.4
Renal transplant	13	481	4	403	3.27	0.07	2.6	1

Comparative analysis of descriptive measures and gender was demonstrated in Table 4 as mean values. The mean Height and Weight for males were 67.8 kg and 164 cm and for females were 61.2 kg and 154 cm, respectively.

On analysis of their lab investigation values, males had a mean Hemoglobin of 11.8 g/dl; mean Platelet counts of 270.64 per mm^3; mean white cell counts of 7.48 x 10^9/L; mean neutrophils count of 3.9 x 10^9/L and mean lymphocytes count of 2.35 x 10^9/L whereas females had mean Hemoglobin of 11.1 g/dl; mean Platelet counts of 285.22 per mm^3; mean white cell counts of 6.93 x 10^9/L; mean neutrophils count of 3.9 x 10^9/L and mean lymphocytes count of 2.25 x 10^9/L. The mean values for the renal function test such urea, which were 7.16 mmol/L in males and 5.6 mmol/L females, for creatinine, which were 124.7 umol/L in males and 141.4 umol/L females and eGFR was 77 ml/min/1.73m^2 in males and 80 ml/min/1.73m^2 in females. The inflammatory markers like C-reactive protein, ESR, C3 and C4 levels and electrolytes including sodium, potassium, calcium, and phosphate measured were all comparable between both males and females.

Table 4: Shows the comparative analysis of patients by gender among demography and Laboratory investigations.

	Male (494) 54.82%	Female (407) 45.17%	Values
Descriptive measures	Mean (S.D)	Mean (S.D)	p
Age (years)	45.92 (19.6)	44.62 (19.5)	0.32
Weight (kg)	67.83 (19)	61.19 (18.9)	<0.001
Height (cm)	164.33 (12)	154.26 (11.6)	<0.001
BMI	24.94 (5.7)	25.68 (7)	0.08
Hemoglobin	11.82 (2.5)	11.1 (1.9)	0.03
Platelets	270.64 (129.7)	285.22 (120.5)	0.08
White cell counts	7.48 (5.2)	6.93 (3.8)	0.07
Neutrophils count	3.9 (2.7)	3.91 (2.9)	0.95
lymphocytes	2.35 (2.8)	2.25 (3.7)	0.64
C-reactive protein	41.14 (54.8)	35.77 (44.2)	0.28
ESR	37.37 (38)	46.19 (38.9)	<0.001
C3	1198.1 (287.6)	1279.9 (347)	0.22
C4	294.62 (128.6)	300.74(164.5)	0.84
ALT	29.38 (27.8)	28.99 (54.7)	0.89
Albumin	34.3 (8)	33.63 (7.2)	0.19
G-gap	39.72 (14.8)	39.81 (13.3)	0.92
Sodium	136.81 (3.6)	136.75 (3.9)	0.82
Potassium	4.28 (0.5)	4.15 (0.5)	0.5
Serum bicarbonate	23.4 (3.5)	22.92 (3.5)	0.04
Serum urea	7.16 (6.2)	5.6 (5.1)	0.01
Serum creatinine	124.79 (93.2)	141.44 (115.8)	<0.001

From Table 5, it shows that 866 patients out of 901 had chronic kidney disease staged from 1 to 5 as per National Kidney foundation used in the hospital, of which 476 (55%) were males and 390 (45%) were females. The remaining 35 patients were recorded to have normal renal functions with no proteinuria in urine analysis. As depicted in Figure 1 and Figure 2, a total of 552 patients were categorized to have stage 1 CKD with the mean serum β-2M (mg/dl) levels found to be 3.04(5) in 287 male patients and 2.68(3.9) in 265 female patients. For those with stage 2 CKD, a total of 121 patients with 69 males and 52 females had their mean Beta2 levels 4.15 (2.9) and 4.06 (3.3) respectively. There was a total of 91 patients with Stage 3 CKD, of which 61 were males and 30 were females, with their mean serum β-2M levels being 7.14 (5.3) and 8.96 (7.2) respectively. There was a total of 57 patients with stage 4 CKD consisting of 34 males and 23 females whose mean serum β-2M levels were 18.38 (18.3) and 13.42 (12) respectively. Lastly there were 45 patients with Stage 5 CKD of which 25 were male patients and 20 were female with a mean serum Beta2 level of 27.93 (18.1) in the males and 23.91(15.2) in the females. Overall, there is a clear upward trend where the higher the stage of chronic kidney disease, the higher the average serum β-2M values.

The serum β-2M levels were compared against various variables as presented in table 6, where it shows that males had a mean value of 6.04 while females had a mean of 4.94.

In the 692 patients from the Hemato-oncology department, the mean levels were 4.59 as compared to the 54 patients from the Nephrology department who had a mean of 18.69.

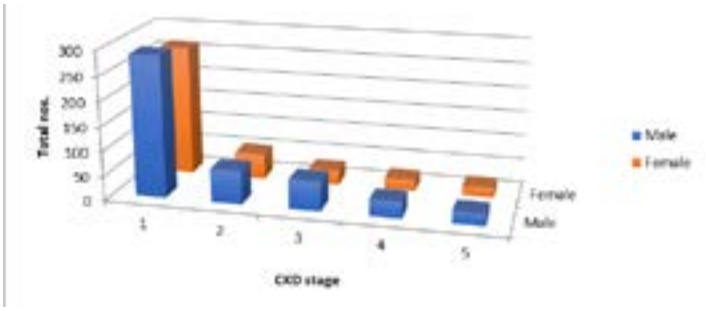
The 192 patients diagnosed with Multiple Myeloma had a mean level of 8.51, however, the 400 patients diagnosed with Lymphoma had mean level of 2.93.

The varying levels of serum Beta2 levels depending on the presence of comorbid conditions is portrayed in Figure 3, online supplementary file. Patients with Diabetes had a mean value of 7.41; Hypertensive patients had a mean of 8.59 and patients with dyslipidemia had a mean of 6.81, which were higher as compared to those who did not have the conditions. Those with a diagnosis of autoimmune disorders showed a higher mean serum Beta2 microglobulin level however, with the presence of ANA, Anti ds DNA, Rheumatoid factor and ENA the mean levels were lower. Malignancy in both hematological and non-hematological patients had lower mean levels of 4.81 and 4.72 respectively. Presence of chronic infections such as HIV and Hepatitis B increased the mean values to 9.93 and 7.2 and were much higher compared to those who tested negative while patients with Hepatitis C had a mean value of 4.02. However, a presence of WBC or RBC in urine increased the mean serum β-2M levels to 8.92 and 10.37 respectively. Patients of End-stage kidney disease on renal replacement therapy, a total of 17 patients, had a mean value of 18.79 that was about three times as high compared to patients who did not have End-stage kidney disease.

Table 5: Shows the distribution of serum Beta2 microglobulin levels according to different stages of CKD.

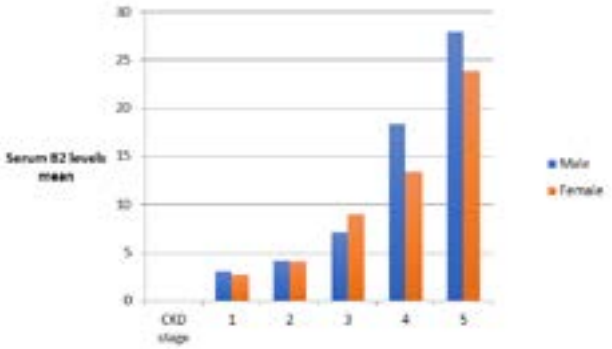
	Serum Beta2 microglobulin levels			Sample size				
	Male	Female	Values	Male	Female	(Males+ Females)	Values	
CKD stage	Mean (S.D)	Mean (S.D)	p				Chi2	Pr
1	3.04 (5)	2.68 (3.9)	0.34	287	265	552	8.04	0.09
2	4.15 (2.9)	4.06 (3.3)	0.87	69	52	121		
3	7.14 (5.3)	8.96 (7.2)	0.17	61	30	91		
4	18.38 (18.3)	13.42 (12)	0.26	34	23	57		
5	27.93 (18.1)	23.91 (15.2)	0.46	25	20	45		
				Total (Males)	Total (Females)	Total (Males+Females)		
				476	390	866		

Figure 1: Shows a total of 552 patients were categorized to have chronic kidney disease stage 1-5.



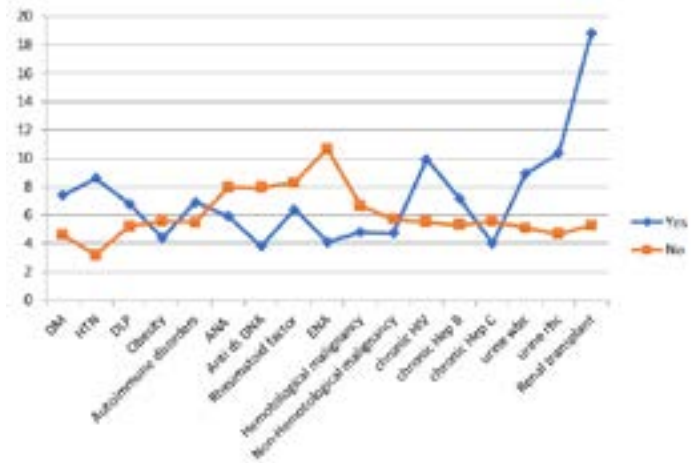
CKD stage	Male	Female	Total (Male+Female)
1	287	265	552
2	69	52	121
3	61	30	91
4	34	23	57
5	25	20	45
	Total (Male)	Total (Female)	
	476	390	

Figure 2: Shows the mean serum Beta2 microglobulin (mg/dl) levels of chronic kidney disease stage 1-5.



	Mean Serum B2 macroglobulin levels	
CKD stage	Male	Female
1	3.04	2.68
2	4.15	4.06
3	7.14	8.96
4	18.379	13.42
5	27.936	23.91

Figure 3: Shows the serum B2 levels across various medical comorbidities.



5. Discussion

This is the first study to evaluate all serum measurements of β-2M for the whole country across various ages, gender, medical conditions, and medical departments. The study sample overall had patients in middle age with similar sex distribution, shorter in height and lighter in weight. Majority of the patients had an eGFR above 60 ml/min/m2 with 75% of cases occurring in CKD stages I-II. Serum β-2M levels tend to increase with increasing CKD stages in both the male and female patients. Hematological malignancies have higher serum β-2M levels. Also, chronic infections tend to have high β-2M serum levels and the levels gets higher with the presence of urinary WCC and blood cells. Management strategies for various hematological disorders, particularly during chemotherapy administration, need to take into consideration maintenance of a good kidney function especially improvement of

hydration and the acid base control.

The β-2M, is a protein of low molecular weight that is easily sieved by the vasculature of glomeruli, reabsorbed in the kidney tubules and destroyed [5,24]. The quantity of β-2M in the serum is quite small in the healthy population. β-2M was first discovered in 1964 in the urine of subjects with Wilson's disease or cadmium poisoning [25,26]. During 1980, it was initially proposed as a biomarker for glomerular filtration. However, the level increases in case of inflammatory, immunologic, and neoplastic events. But the early identification of patients at a high risk of renal dysfunction is of great importance as it may allow specific measures to be taken to delay renal impairment, or as an acute phase reactant that increases in a variety of inflammatory and infectious disorders [27].

β-2M consists of 100 amino-acids solitary polypeptide chain, with a globular structure preserved by a disulfide bond- linking two cysteine in positions 25 and 80 [28,29]. It is a protein of relatively small molecular weight and is encoded by a gene in chromosome 15 in humans [28,29]. In healthy populations, the daily endogenous manufacture of β-2M is approximately 150 to 200 mg [30,31]. It is readily filtered through the kidney glomeruli and almost completely reabsorbed and destroyed by proximal tubular cells, with less than 400 ng of intact f32m appearing daily in the urine [30,31].

A panel of members of the 2009 International Myeloma Workshop developed guidelines for risk stratification in multiple myeloma. They found that high serum β (2)-microglobulin level and International Staging System stages II and III, incorporating high β (2)-microglobulin and low albumin, are considered to predict higher risk disease [32]. β-2M levels are sex, race, and ethnicity dependent where old age population have higher serum levels. In the present study, the mean age was 45.9 years for males and 44.6 years for females. However, it has been shown that it is less influenced by age, sex, and race than serum creatinine and provides a less accurate estimate of GFR than the CKD-EPI equation [33]. The β-2M serum levels increase in solid organ malignancies, hematological malignancies including lymphoproliferative disorders such as myeloma, lymphoma (Hodgkin and non-Hodgkin) and chronic lymphoblastic leukemia, as well as many autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [34]. Its production is encouraged by several situations such as monoclonal or polyclonal stimulation, spread of lymphoid cells such as malignant tumors, lymphoproliferative B cell disorders and chronic inflammatory diseases including viral infections, viral hepatitis, systemic lupus erythematosus, rheumatoid arthritis [34]. All these are conditions, under which one would expect a higher number of cells bearing MHC molecules to be generated, or conditions in which higher shedding of β-2M is seen as shown in the present study.

The β-2M is routinely measured in many clinical laboratories by a variety of methods – nephelometry, turbidimetry or immunoassay [35]. In hematological malignancies such as leukemia, lymphoma and multiple myeloma, serum β-2M levels are found to be elevated despite a preserved renal function as seen in our patients where majority have normal kidney function [34]. In the present study, the majority of malignancies where β-2M levels were recorded were the hematological malignancies with a serum level of 4.81 compared to non-hematological malignancies with a serum β-2M of 4.72. It has been reported that 60% of patients with mantle cell lymphoma have high pretreatment serum β-2M levels. The elevated levels are independently associated with unfavorable prognosis of most of the hematological malignancies as higher serum levels of β-2M prognostically reflect a higher tumor burden or a more aggressive myeloma subtype [9,17].

Rajkumar et al found that low beta2-microglobulin (< or =2.7 mg/l) was associated with a significantly better complete response rate compared with high levels (54 vs 19%, P = 0.002) [36] However, it has a prognostic value on the progression of asymptomatic disease and the outcomes after stem cell transplantation [37,38]. Rajkumar et al reported that major prognostic factors in myeloma and the evidence supporting their usefulness in clinical practice and research, which included the serum beta 2-microglobulin [38]. The International Staging System has utilized it for its staging where Stage I: β-2M serum level < 3.5 mg/dl and albumin > 3.5 g/dl, Stage II: β-2M serum level > 3.5 but less than 5.5 mg/dl or β-2M serum level < 3.5 mg/l and albumin < 3.5 g/dl, Stage III β-2M serum level > 5.5 mg/l [39].

In Oman, the health system is very good and free to all its people and has been highly acknowledge and judged by the world Health Organization [40,41]. All investigations and evaluations are done routinely for free. In the present studies, most patients are in early stages of CKD, but it has been shown that even patients with early disease stage have elevated serum levels of β-2M, which may reflect a more aggressive behavior of the malignant process. This may reflect the combination of higher tumor burden and more aggressive biology, and it is supported by observations that higher serum levels of β-2M are associated with a shorter time to therapy [42]. In addition, failure to normalize β-2M serum level after 6 months of kinase inhibitor therapy may be associated with poorer progression-free survival [HR 16.9 (95% CI: 1.3–220.0)] for ibrutinib-treated patients. This association persisted after multivariate adjustments [43].

Also, the present study found that serum β-2M is high in non-hematological solid cancers, such as ovarian cancer, gall bladder cancer, prostate cancer, breast cancer, and renal cell carcinoma. Its higher value is closely related to the poor prognosis and aggressive characteristics of the tumor [44]. Due to the high prevalence of high β-2M in patients with ovarian cancer, β-2M has been incorporated into the FDA approved OVA1 multi-analysts assay for risk stratification of adnexal masses. OVA1 measures the serum levels of five analysts, CA125, transthyretin, apolipoprotein-A1, transferrin, and β-2M [45]. Results are reported as high or low risk for ovarian cancer and are used to determine whether referral to gynecologic oncology is required prior to surgical treatment of an adnexal mass. In addition, it is found to be a global biomarker of occult malignancy [HR: 1.25 (95% CI: 1.06–1.47; for the trend of higher risk with increasing β-2 M quartile)], and to a lesser extent colorectal cancer risk [HR: 2.21 (95% CI: 1.32–3.70; for the trend of higher risk with increasing β-2M quartile)] [34]. These associations were not attenuated after adjustment for an inflammatory biomarker, CRP, or even renal function (eGFR) in 12,300 patients as noted in the prospective ARIC study. Significant associations were also observed for mortality of lung, and hematological cancers [34]. In the present study, CKD patients accumulate β-2M as kidney function diminishes and CKD progresses where end-stage kidney disease has the highest β-2M. The ESRD accumulated β-2M has been conventionally attributed to impaired removal secondary to decreased glomerular

filtration at the kidney level. However, it could also be due to an interference of uremic toxins with the non-covalent binding of β-2M to MHC molecules, leading to an increase in shedding of β-2M into the circulation. β-2M is positively correlated with serum creatinine with a Pearson coefficient of 0.78 and negatively correlated with GFR with a Pearson coefficient of 0.8 (13).

Middle molecule toxins have troubled nephrologists for long and it has led to the development of various techniques using β-2M for the approximation of these toxin [33]. Therefore, ESRD on dialysis may have serum β-2M levels of up to 60 times as that of normal value [33]. Among the hemodialysis population, the amyloid presence or deposits in the tissue was shown in carpal tunnel syndrome surgical tissue removal (46). Dialysis related amyloidosis (DRA) is a general complication of dialysis for end-stage kidney disease. The amyloid fibrils consist of β-2M structure especially f32m amyloids (A/32m) [47]. Among hemodialysis, the amount of Af32m in the joints is very high with almost 25% of patients being affected within a few years post dialysis and can reach higher than 90% after 7 years of dialysis in both vertebrae and peripheral joints. It is also noted that the sternoclavicular joints and the cervical vertebrae are preferentially involved compared with shoulders or thoracic vertebrae [46]. Hence, there is a good argument to reduce β-2M towards normal serum levels from a clinical perspective among patients with ESRD especially those treated with maintenance hemodialysis.

The β-2M levels are increased in various autoimmune diseases including SLE and rheumatoid arthritis. In the present study, studies the β-2M levels occur in these diseases and also examined the levels by ANA, RF, ENA and dsDNA. The positivity of these serum antibodies indicates an active disease and hence higher β-2M levels represent more shedding of cells. The serum levels of β-2M could decrease after therapy and control of inflammation. The serum levels also correlate with overall kidney disease activity scores and proteinuria [34]. In addition, as shown in the present study, the presence of hematuria - which indicates glomerulonephritis, has high levels of β-2M.

In autoimmune disorders, the importance of monitoring of β-2M serum levels to assess disease activity has been highlighted lately. This study revealed that increased β2M levels were found in at least one third of SLE patients and correlated with the disease activity markers such as SLEDAI-2K, anti-dsDNA antibodies titer, and C4 component [48]. In addition, high serum level of β-2M is associated with musculoskeletal system involvement, hematological symptoms and vasculitis. Also, high β-2M serum levels are reported in patients with serositis, oral erosions and symptoms of autoimmune disorders. Wakabayashi et al. proved that β-2M concentration decreased throughout the course of immunosuppressive treatment [49]. The cause of elevated β-2M concentration in autoimmune disorders such as SLE patients is not fully understood. Some researchers suggest the β-2M increase may result from increased lymphocyte turnover in autoimmune disease, or the presence of immune complexes formed by β-2M with anti- β-2M antibodies removed by kidneys resulting in a lower percentage of kidney damage [48].

Infection may be associated with high β-2M serum levels. In the present study, infections such as HIV have a high serum β-2M level. Based on the analyses of data in 1378 patients through multivariate logistic regression, a predictive model of first TE grade ≥ 3 infection in the first 4 months retained Eastern Cooperative Oncology Group performance status and serum β_2-microglobulin, lactate dehydrogenase, and hemoglobin levels to define high- and low-risk groups showing significantly different rates of infection (24.0% vs. 7.0%, respectively; $P < 0.0001$) [50]. A high serum level of β-2M was detected in many infectious diseases including HCV [51]. Serum β-2M was elevated in HIV and hepatitis infections compared to healthy population [52]. High serum β-2M levels are associated with an activated immune response and are released by activated lymphocytes (T4/T8 cells), so an increase in its levels might indicate increasing infection replication related cell death [52]. In hepatitis chronicity, many differentially expressed genes involved in the pathways of the immune system, fibrosis, proliferation, cell growth, and apoptosis have been found to be upregulated, including major histo-compatibility and β-2M genes [18,52]. Serum β-2M levels were significantly higher in severe hepatic inflammation, where high numbers of activated cytotoxic T cells were found along with marked hepatocellular expression of β-2M [52].

6. Conclusion

Higher β-2M generation comes from high cell turnover, e.g., as in oncological conditions, and from altered cell binding of β-2M to the many proteins. The stage of kidney function is the main determinant of serum plasma level of β-2M by affecting both filtration via glomeruli of the kidney and the generation of β-2M. In addition, interference with the binding of β-2M to MHC and non-classical MHC molecules by various uremic solutes that are retained in kidney failure institutes a key cause for the sharp increase of β-2M in CKD. β-2 M is a promising marker to assess glomerular and tubular function in adults. It has similar performance to the Cr-based estimating equations as a measure of kidney function but may be more strongly associated with cardiovascular morbidity and mortality than serum creatinine, or other small molecular kidney filtration markers. Management strategies for various hematological disorders need to take into consideration maintenance of a good kidney function especially improvement of hydration and the acid base control.

6.1. Disclosure of potential conflicts of interest:

The study was approved by the Scientific Research Committee and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments ethical standards. https://mohcsr.gov.om/my-researches/

6.2. Consent for publication: All authors have agreed to the publication and to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

6.3. Data availability statement: Data can be provided upon request on individual basis
but it is not available publicly.

6.4. Competing interests: All authors declare no conflict of Interest related to the current manuscript.

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