Prognostic Value of Transgelin-2 As A Predictor of Renal Affection in Multiple Myeloma at Benha University Hospital

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Abstract

Background: Multiple myeloma (MM) is a malignancy of clonal plasma cells accounting for approximately 10% of haematological malignancies and 1.8% of all malignancies. Transgelin-2 was found to be a marker of interstitial fibrosis, glomerulosclerosis, and renal damage. The aim of this work was to evaluate the serum transgelin-2 as a predictor of renal impairment in patient with multiple myeloma and to determine the effect of transgellin-2 of chronic kidney disease patients with multiple myeloma.

Methods: This observational case control study was conducted on 52 participants with MM with chronic kidney disease (CKD).

Patients were divided equally into two groups: Case group: included patients with MM with or without CKD and control group: included only CKD patients. serum transgelin-2 levels were assessed in all patients using suitable ELISA kits.

Results: Serum Transgelin-2 was significantly higher in case group compared to control group (P=0.010). There was a significant positive correlation between serum Transgelin-2 and ALT (r=0.779, P<0.001), blood glucose (r=0.810, P<0.001), serum creatinine (r=0.655, P<0.001) and uric acid (r=0.316, P<0.001). There was a significant negative correlation between serum Transgelin-2 and Weight (r= -0.327, P=0.018) and estimated glomerular filtration rate (eGFR) (r= -0.774, P<0.001). Serum Transgelin-2 was a significant predictor of the renal affection at

AUC of 0.715, P value of 0.038, and at cut off value ≤0.30 ng/mL, with 80.85% sensitivity, 40.0 % specificity, 92.7% PPV and 18.2%NPV. The multiple regression analysis revealed that hsCRP, serum creatinine, and serum Transgelin-2 were the only significant predictor of the level of eGFR. The multiple regression analysis revealed that, eGFR, and serum Transgelin-2 were the only significant predictor of the level of serum creatinine level.

Conclusions: Serum Transgelin-2 levels were significantly higher in the MM group and exhibited positive correlations with markers of liver function, blood sugar, kidney function, and uric acid, while demonstrating negative correlations with weight and eGFR. Notably, Transgelin-2 emerged as a significant predictor of renal affection with promising sensitivity and specificity.

Keywords: Transgelin-2, Renal Affection, Multiple Myeloma, Chronic Kidney Disease

Introduction:

Multiple myeloma (MM) is a malignancy of clonal plasma cells accounting for approximately 10% of haematological malignancies and 1.8% of all malignancies [1]. Because of complicated pathogenesis, and multiple end organ effects, patients with multiple myeloma are treated by multidisciplinary teams from many areas of medicine, including haematology, oncology,[2]. Despite being a disease of population (median age 70 years old), approximately 10% of patients are under 50 years old [3].

Renal impairment (RI) is a common complication of multiple myeloma (MM), around 50% of patients of multiple myeloma have renal impairments at presentation, and up to 5% require dialysis treatment. Severe acute kidney injury as a cause of renal impairment is a particular challenge as historically the survival of patients who sustain this complication and require dialysis is very poor [4].

Kidney injury is a common complication of multiple myeloma and other plasma cell dyscrasias, and it is associated with increased mortality. Multiple pathogenic mechanisms can contribute to kidney injury in the patient with myeloma, some of which are the result of nephrotoxic monoclonal Ig and some of which are independent of paraprotein deposition [5].

The three most common forms of monoclonal Ig-mediated kidney disease are cast nephropathy, monoclonal Ig deposition disease (MIDD), and AL amyloidosis. The term myeloma kidney refers to cast nephropathy and should not be used to refer to the entire spectrum of renal failure and myeloma. Beyond these three forms, glomerulonephritis (GN) with active urinary sediment can occur in a membranoproliferative, diffuse proliferative, cryoglobulinaemic, or crescentic pattern [6].

Renal impairment in patients with multiple myeloma is commonly associated with excess monoclonal free light chain production. Myeloma cast nephropathy is the predominant renal

pathology in patients presenting with severe renal impairment secondary to acute kidney injury (AKI) [4].

Transgelin-2 is a protein involved in cytoskeletal organization and expressed in smooth muscle tissue. According to animal studies it's a potential mediator of kidney injury, fibrosis, and moreover, its role in tumorigenesis is emerging in a variety of cancers. [7].

Transgelin-2 was found to be a marker of interstitial fibrosis, glomerulosclerosis, and renal damage.it is upregulation depends on the etiology of the disease in various cells (glomerular, parietal or visceral, or tubular interstitial cells) and elevated expression was detected in both glomerular and tubulointerstitial cell injury [8].

The aim of this work was to evaluate the serum transgelin-2 as a predictor of renal impairment in patient with multiple myeloma and to determine the effect of transgellin-2 of chronic kidney disease patients with multiple myeloma.

Patients and Methods:

This observational case control study was conducted on 52 participants with multiple myeloma with or without CKD with CKD patients, who also accepted to response the questionnaires from December 2022 to December 2023.

An informed written consent was obtained from the patients. The study was done after approval from the Ethical Committee of Benha University Hospital.

Exclusion criteria were Patients or their guardian refusal to share in the study, or cancers other than myeloma.

Patients were divided equally into two groups: Case group (n=26): included patients with multiple myeloma with or without CKD and ccontrol group (n=26): included only CKD patients.

The following data was recorded in all patients: History taking and demographic data collection (Age, sex, smoking habit, Medications and Past history of any medical condition or previous

hospital admission), clinical examination, and laboratory investigations (Complete blood count, Renal function test (urea, serum creatinine), glomerular filtration rate, calcium, potassium, serum transgelin-2).

Procedure

five millilitres of venous blood sample were collected from every participant in the study under complete aseptic precautions in the plain test tubes without anticoagulant, samples were allowed to clot for 30 minutes before centrifugation for 10 minutes at approximately 3000xg. Serum was removed and stored at -80°C until assay time using suitable ELISA kits for estimation of serum transgelin-2 level.

Test principle

The microtiter plate provided in this kit has been pre-coated with an antibody specific to TAGLN2. Calibrators or samples are then added to the appropriate microtiter plate wells with a biotin-conjugated antibody preparation specific for TAGLN2. Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. Then a TMB substrate solution is added to each well. Only those wells that contain TAGLN2, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of a sulfuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 10 nm. The concentration of TAGLN2 in the samples is then determined by comparing the O.D. of the samples to the calibration curve.

Statistical analysis

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by unpaired student t-test. Quantitative non-parametric data were presented as the median and

interquartile range (IQR) and were analysed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analysed using the Chi-square test or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant. Pearson or spearman correlation was performed to estimate the degree of correlation between two quantitative variables. The overall diagnostic performance of each test was assessed by ROC curve analysis and evaluation of diagnostic sensitivity, specificity, positive Predictive value (PPV) and negative Predictive value (PPV). The area under the curve (AUC) evaluates the overall test performance.

Results:

The baseline characteristics (age, sex, weight, height, and BMI), associated comorbidities (hypertension, diabetes mellitus and hyperlipidaemia), and clinical examination of vital sign (HR, SBP and DBP) were insignificantly different between both groups. **Table 1**

Table 1: Baseline characteristics, Comorbidities and Clinical examination of vital signs of the studied patients

		Total (n=52)	Case group (n=26)	Control group (n=26)	P value
Age (years)	**Mean± SD**	59.1 ± 11.1	58.5 ± 7.68	59.7 ± 11.73	0.656
	Range	39 – 77	48 - 77	39 - 73	
Sex	**Male**	27 (51.92%)	12 (46.15%)	15 (57.69%)	0.405
	Female	25 (48.08%)	14 (53.85%)	11 (42.31%)	
Weight (Kg)	**Mean± SD**	71.8 ± 7.35	72.5 ± 8.15	71.04 ± 7.75	0.522
	Range	59 – 85	61 - 85	59 - 85	
Height (m)	**Mean± SD**	1.65 ± 0.03	1.66 ± 0.04	1.64 ± 0.03	0.235
	Range	1.59 - 1.7	1.59 - 1.7	1.6 - 1.7	
BMI (Kg/m^2)	**Mean± SD**	26.4 ± 2.81	26.5 ± 3.18	26.3 ± 3.05	0.862
	Range	20.42 - 32.39	21.45 - 31.25	20.42 - 32.39	
Hypertension		25 (48.08%)	11 (42.31%)	14 (53.85%)	0.405
Diabetes mellitus		14 (26.92%)	6 (23.08%)	8 (30.77%)	0.532
Hyperlipidemia		15 (28.85%)	7 (26.92%)	8 (30.77%)	0.759
HR (beats/min)	**Mean± SD**	85.3 ± 6.74	83.9 ± 6.53	86.8 ± 6.95	0.129
	Range	75 – 95	75 - 95	75 - 95	
SBP (mmHg)	**Mean± SD**	137.5 ± 13.91	139.2 ± 14.9	135.8 ± 13.91	0.391
	Range	110 – 160	110 - 160	110 - 160	
DBP (mmHg)	**Mean± SD**	80.4 ± 7.51	80.0 ± 8.0	80.8 ± 7.44	0.721
	Range	70 – 90	70 - 90	70 – 90	

Data are presented as mean ± SD or frequency (%). BMI: Body mass index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure.

There was an insignificant difference between both groups regarding the time since diagnosis, CKD , Hb, PLT, WBCs, RBS, calcium, sodium, potassium ALT, AST, total protein, albumin, β2-microglobulin, hsCRP and lactate dehydrogenase. Serum M protein was significantly lower in case group compared to control group (P=0.018). **Table 2**

Table 2: The time since diagnosis, CKD, laboratory investigations, hsCRP and lactate dehydrogenase of the studied groups

		Total (n=52)	Case group (n=26)	Control group (n=26)	P value
Time since diagnosis (months)	**Mean± SD**	35.5 ± 14.66	37.5 ± 13.84	33.5 ± 13.2	0.296
	Range	14 – 59	14 – 59	14 – 58	
CKD	**Free from CKD**	5 (9.62%)	5 (19.23%)	0 (0%)	0.221
	Stage 1	7 (13.46%)	3 (11.54%)	4 (15.38%)	
	Stage 2	16 (30.77%)	7 (26.92%)	9 (34.62%)	
	Stage 3	12 (23.08%)	6 (23.08%)	6 (23.08%)	
Hb (g/dL)	**Mean± SD**	10.7 ± 6.91	11.6 ± 7.66	9.9 ± 1.56	0.260
	Range	7.5 – 48	7.5 – 48	7.7 – 12	
PLT (*10^9/L)	**Mean± SD**	236.8 ± 40.73	230.3 ± 39.42	243.3 ± 43.17	0.264
	Range	170 – 300	170 – 292	173 – 300	
WBCs (*10^9/L)	**Mean± SD**	8.4 ± 1.65	8.6 ± 1.63	8.1 ± 1.56	0.275
	Range	6 – 11	6 – 11	6.1 – 11	
RBS (mg/dL)	**Mean± SD**	144.6 ± 44.74	153.4 ± 52.92	135.7 ± 41.4	0.185
	Range	48 – 310	48 – 310	90 – 230	
Calcium (mg/dL)	**Mean± SD**	2.7 ± 0.49	2.6 ± 0.32	2.7 ± 0.54	0.641
	Range	2 - 3.7	2.2 - 3.4	2 - 3.7	
Sodium (mEq/L)	**Mean± SD**	137.98 ± 4.84	137.5 ± 4.96	138.5 ± 4.57	0.436
	Range	129 – 145	129 – 144	129 – 145	
Potassium (mEq/L)	**Mean± SD**	5.1 ± 0.91	4.96 ± 0.57	5.32 ± 0.92	0.096
	Range	4.2 - 6.9	4.2 - 6.7	4.2 - 6.9	
ALT (U/L)	**Mean± SD**	31.2 ± 5.91	31.3 ± 5.62	31.1 ± 6.13	0.888
	Range	20 – 40	21 – 39	20 – 40	
AST (U/L)	**Mean± SD**	23.7 ± 3.96	23.9 ± 3.31	23.5 ± 4.15	0.713
	Range	18 – 30	18 – 29	18 – 30	
Total protein (g/dL)	**Mean± SD**	5.5 ± 2.03	5.7 ± 1.98	5.4 ± 2.02	0.664
	Range	2.6 - 8.4	2.6 - 8.4	2.6 - 8.4	
Albumin (g/dL)	**Mean± SD**	4.6 ± 0.68	4.5 ± 0.73	4.7 ± 0.66	0.514
	Range	3.6 - 5.9	3.6 - 5.7	3.7 - 5.9	
Serum M protein (g/dL) only cases	**Mean± SD**	1.5 ± 1.11	1.2 ± 1.25	N/A	0.018*
	Range	0.18 - 3.55	0.18 - 3.55	N/A	
	Median (IQR)	1.3 (0.34-2.47)	0.37 (0.25-1.9)	N/A	
β2-microglobulin (g/dL)	**Mean± SD**	30.4 ± 4.87	35.6 ± 28.07	25.3 ± 4.84	0.405
	Range	17 - 120.3	18.2 - 120.3	17 - 32.1	

	Median (IQR)	26.3 (22.1-30.2)	26 (22.9 - 30.6)	26.8(20.6 -28.4)	
hsCRP (mg/L)	**Mean± SD**	26.4 ± 12.12	25.2 ± 13.65	27.5 ± 11.53	0.527
	Range	5 - 49.7	5 - 49.7	9 - 46.5	
Lactate dehydrogenase (IU/L)	**Mean± SD**	322.3 ± 47.65	318.0 ± 61.9	326.5 ± 39.21	0.557
	Range	150 – 399	150 – 399	250 – 388	

Data are presented as mean ± SD or frequency (%). CKD: chronic kidney disease. Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, RBS: random blood sugar, ALT: alanine aminotransferase, AST: aspartate aminotransferase, hsCRP: high sensitivity c-reactive protein. *Significant as p-value ≤ 0.05.

Regarding the ISS of patients in the case group, 11 (42.31%) patients were stage I, 5 (19.23%) patients were stage II and 10 (38.46%) patients were stage III. The Immunofixation of patients in the case group had identified the following immunoglobulins: IgG in 12 (46.15%) patients, IgM in 1 (3.85%) patient, IgA in 2 (7.69%) patients, κ in 6 (23.08%) patients and λ in 5 (19.23%) patients. **Table 3**

Table 3: ISS and Immunofixation of patients in the case group

		Case group (n=26)
ISS	**Stage I**	11 (42.31%)
	Stage II	5 (19.23%)
	Stage III	10 (38.46%)
Immunofixation	**IgG**	12 (46.15%)
	IgM	1 (3.85%)
	IgA	2 (7.69%)
	K	6 (23.08%)
	Λ	5 (19.23%)

Ig: immunoglobulin, ISS: international staging system.

Serum creatinine and total cholesterol were significantly lower in case group compared to control group (P<0.001 and 0.026 respectively). Serum Transgelin-2 was significantly higher in case group compared to control group (P=0.010). There was an insignificant difference between both groups regarding uric acid, BUN, eGFR, triglycerides, HDL and LDL.

Table 4: Serum Transgelin-2 level among ISS stages of the case group

		Stage I (n=11)	**Stage II (n=5)**	**Stage III (n=10)**	**P value**
Serum Transgelin-2 (ng/mL)	**Mean± SD**	0.20 ± 0.06	0.24 ± 0.11	0.27 ± 0.09	0.235
	Range	0.13 - 0.30	0.12 - 0.39	0.13 - 0.39	

*: statistically significant as p value ≤0.05.

Serum Transgelin-2 is a significant predictor of the renal affection at AUC of 0.715, P value of 0.038, and at cut off value ≤0.30 ng/mL, with 80.85% sensitivity, 40.0 % specificity, 92.7% PPV and 18.2%NPV. **Table 7 and Figure 1**

Table 5: Diagnostic accuracy of serum Transgelin-2 for prediction of renal affection

	Cut off	Sensitivity	Specificity	PPV	NPV	AUC	P value
Transgelin-2 (ng/mL)	≤0.30	80.85	40.00	92.7	18.2	0.715	**0.038***

PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, *: statistically significant as p value ≤0.05.

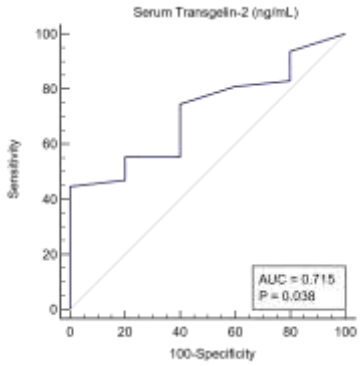

Figure 1: ROC curve analysis of serum Transgelin-2 for prediction of renal affection

The multiple regression analysis revealed that, hsCRP, serum creatinine, and serum Transgelin-2 were the only significant predictor of the level of eGFR.

Discussion

According to the Global Burden of Disease 2016 study, the worldwide age-standardized incidence and death rate of multiple myeloma (MM) are estimated at 2.1 and 1.5 per 100,000 individuals, respectively [9].

MM is a proliferative plasma cell disorder that is more prevalent in the aging population and presents itself with characteristic features of organ involvement: bone lesions, anaemia, renal insufficiency, hypercalcemia, and specific malignancy biomarkers (plasma cell clonality ≥60%, involved to uninvolved serum free light chains (FLCs) ≥100 and >1 focal lesion on magnetic resonance imaging) [10].

Severe renal failure is a deleterious condition with a high risk of early death and is one of the major culprits of early mortality. A low treatment response rate and a median survival of 3–4 months was observed prior to the emergence of modern myeloma therapies [11].

Renal insufficiency is considered reversible in about 50% of cases in some reports. With the advent of novel drugs (e.g., proteasome inhibitors), prognosis for MM patients with renal insufficiency has remarkably improved [12].

In clinical routine, the laboratory assessment of renal function usually largely relies on serum creatinine measurements used to estimate the glomerular filtration rates [13].

However, routinely available diagnostic measures (e.g., serum creatinine) are subject to several caveats and do not always allow for early and reliable prediction of ongoing renal damage [14].

Transgelin-2 (SM22), a cytoskeletal actin-binding protein involved in differentiation of smooth muscle cells, osteoblasts, and adipocytes, is present in fibroblasts, some epithelial cells, immune cells, bone marrow cells or stem cells. Basic function of transgelin-2 is participation in cytoskeleton remodelling via its effect on actin regulation [15].

Moreover, transgelin is involved in bone marrow mesenchymal stem cell (MSC) proliferation and differentiation. Recent studies report dysregulation of SM22 in different malignancies and emphasize its role in cancer development and progression. Furthermore, transgelin-2 was found to be a marker of interstitial fibrosis, glomerulosclerosis, and renal damage. Its upregulation depends on the aetiology of the disease in various cells and elevated expression was detected in both glomerular and tubulointerstitial injury [16].

The aim of the study was to evaluate the serum transgelin-2 as a predictor of renal impairment in patient with multiple myeloma and determine the effect of transgellin-2 of chronic kidney disease patients with multiple myeloma. To our knowledge, research at this point is rare where previous studies focused on transgelin-2 oncogenic potential and associations with MM

transformation to plasma cell leukemia (PCL) that emphasize transgelin-2 role as a poor survival marker [17]. However, we were not able to prove the association between serum transgelin concentrations and survival.

In the present study, it was found that baseline characteristics (age, sex, weight, height, BMI comorbidities, the time since diagnosis, were insignificantly different between both groups.

Woziwodzka et al. [18] conducted a prospective observational study included 126 patients with MM. A total of 73 women and 53 men were included, aged 29 to 90 years. Median time since diagnosis (Q1; Q3), months 30 (14; 63). There was no statistically significant difference regarding both group regarding age and sex.

In the present study, it was found that the ISS of patients in the case group, where 11 (42.31%) patients were stage I, 5 (19.23%) patients were stage II, and 10 (38.46%) patients were stage III.

Woziwodzka et al. [18] highlighted that Symptomatic MM was diagnosed in 119 patients, the majority of whom were in ISS stage I 84 (67%), stage II 20 (16%), stage III 15 (12%). The remaining seven patients had smouldering MM.

In the present study, it was found that the Immunofixation of patients in the case group had identified the following immunoglobulins: IgG in 12 (46.15%) patients, IgM in 1 (3.85%) patient, IgA in 2 (7.69%) patients, κ in 6 (23.08%) patients and λ in 5 (19.23%) patients.

The diagnosis of MM is based on haematological analysis, mainly bone marrow biopsy. In clinical practice, kidney biopsy is not a mandatory procedure for selection of the appropriate treatment regimen. Taking into consideration the invasiveness of kidney biopsy, potential kidney injury markers may be a favourable solution for patients with MM. However, our main finding was the association between baseline serum transgelin and final eGFR, which shows that circulating transgelin concentrations predict long-term irreversible kidney insufficiency in patients with MM.

Woziwodzka et al. [18] reported that several immunoglobulins was identified where IgG in 92 (73) patients, IgM in 2 (2) patient, IgA in 23 (18) patients, κ in 79 (63) patients and λ in 44 (35) patients, and free light chains patients18 (14).

In the present study, it was found that serum M protein and creatinine was significantly lower in case group compared to control group (P=0.018) while there was an insignificant difference between both groups regarding the laboratory investigations including Hb, PLT, WBCs, RBS, calcium, sodium, potassium, ALT, AST, total protein, albumin, and β2-microglobulin. There was insignificant difference between both groups regarding lactate dehydrogenase, hsCRP, lactate dehydrogenase, uric acid, BUN and eGFR.

Woziwodzka et al. [18] stated that serum transgelin remained higher in patients than in controls after adjustment for the age difference (p = 0.034). There was insignificant difference among both groups regarding total leukocyte count, Hb, albumin, ALT, AST, β2-microglobulin, and platelets. Serum creatinine was significantly lower in case group compared to control group (P<0.001).

There was an insignificant difference between both groups regarding eGFR test where mean baseline eGFR (CKD-EPICr) was 74 (SD: 24) mL/min/1.73 m^2 and 29 (23%) patients had eGFR <60 mL/min/1.73 m^2. eGFR was above 60 mL/min/1.73 m^2 in 97 patients (77%), between 30 and 60 mL/min/1.73 m^2 in 18 patients (14%) and below 30 mL/min/1.73 m^2 in 11 patients (9%). Meanwhile, uric acid was higher in cases group that controls [18].

This finding may have a pathophysiological explanation. The upregulation of transgelin-2 has been associated with tumorigenesis and cancer development and may vary along with clinical stage and tumor size. Interestingly, several studies revealed higher levels of transgelin-2 in inflammation (i.e., SIRS) and explored SM22 overexpression in the regulation of the NIK transcription and proinflammatory NF-kB-signalling pathways as a modulator of vascular inflammation [19, 20].

These studies suggest that transgelin may be viewed as an anti-inflammatory marker. Taking into consideration the role of interleukin 6 in MM pathogenesis as a growth and survival factor, inhibiting apoptosis in myeloma cells, this may also explain SM22 role in tumorigenesis. This may support the hypothesis that at the beginning of the disease and tumorigenesis, transgelin-2 concentrations are higher [12].

However, a few reports demonstrated that transgelin-2 inhibits the motility of cancer cells by suppressing actin polymerization. Moreover, according to available data, only 2% of patients with SMM develop MM. Further, higher concentrations of transgelin in our patients with SMM may possibly be associated with the fact that they had received no treatment [21].

Transgelin levels were also higher in patients who did not receive any MM treatment before the study. Moreover, the sex of the patients with SMM may play a role in elevated transgelin-2 concentrations as in the studied group transgelin concentrations were higher in men, and SMM/ untreated patients were mostly men [22].

In the present study, it was found that serum Transgelin-2 was significantly higher in case group compared to control group (P=0.010).

Recent findings suggest that transgelin may be a potential player in fibrosis and a marker of kidney injury. It has been investigated in various kidney diseases [22-27].

Moreover, transgelin-2 is involved in bone marrow mesenchymal stem cell (MSC) proliferation and differentiation. Several studies revealed transgelin upregulation in leukaemia and lymphoma cell lines. Although transgelin-2 overexpression has been associated with chemotherapy resistance, the precise mechanism is not known [31].

According to previous studies, overexpressed trangelin-2 gene was found in methotrexate-resistant human choriocarcinoma cells and paclitaxel-resistant human breast cancer cells [31].

Transgelin-2 overexpression has also been linked with poor prognosis, and transgelin-2 has been proposed as a potential treatment target due to its restriction to tumor cells (to the contrary to transgelin type-1) [30].

Experimental data in animal models of anti-glomerular basement membrane nephritis revealed that SM22α expression may reflect structural and functional shifts following injury. Downregulation of podocyte proteins and expression of transgelin may reflect dedifferentiation and transdifferentiation of the injured glomerular epithelium [22, 23].

In chronic renal injury models (5/6 nephrectomy) with early tubulointerstitial injury, SM22α expression is observed early in the peritubular and periglomerular compartments. In the ischemia-reperfusion setting, which mainly affects the tubular epithelium, SM22α expression was noted in the peritubular interstitium [23]. In obstructive nephropathy models, periglomerular fibroblasts were observed as the primary cells with transgelin up-regulation, with subsequent elevation in interstitial fibroblasts [32].

These data show transgelin expression in both glomerular and tubulointerstitial injury, which is not limited to a single cell type and can be considered a general indicator of kidney insult. Taken together, these data suggest that in the chronic cycle of injury, repair and scarring of kidney tissue, transgelin may be a marker that reflects this process.

In line with this data, Woziwodzka et al. [18] revealed that studied MM patients presented with significantly higher serum concentrations of transgelin and interleukin 6, and higher urinary concentrations of IGFBP-7 and TIMP-2 even adjustment for the age difference ($p = 0.034$).

Median serum transgelin in the whole studied group was 84.1 ng/mL Transgelin concentrations were higher in men (median 96.2 versus 78.8 ng/mL), in patients with smoldering MM (median 149.2 versus 82.4 ng/mL; $p = 0.003$) and in treatment-naïve patients (median 145.2 versus 82.5 ng/mL; $p = 0.014$); however, the majority of patients with smoldering MM (5 out of 7) and treatment-naïve patients (6 out of 8) were men. Of interest, serum transgelin was higher in

healthy women than in men (control group; median 83.4 vs 60.5 ng/mL, respectively; p = 0.011) [18].

The sex-related difference could not be attributed to differences in MM stage, kidney function or treatment as these were not different between men and women (data not shown). Sex-related differences in circulating transgelin, however, have been reported by others. The proteomic analysis of human plasma published by Silliman at al. revealed 14-fold higher transgelin concentrations in males than in females [33]. Animal studies also reported sex-related differences in the expression of transgelin [34].

In the present study, it was found that there was a significant positive correlation between serum Transgelin-2 and ALT (r=0.779, P<0.001), blood glucose (r=0.810, P<0.001), serum creatinine (r=0.655, P<0.001) and uric acid (r=0.316, P<0.001) while there was a significant negative correlation between serum Transgelin-2 and Weight (r= -0.327, P=0.018) and eGFR (r= -0.774, P<0.001). There was an insignificant correlation between serum Transgelin-2 and other parameters. The multiple regression analysis revealed that Haemodialysis, hsCRP, serum creatinine, and serum Transgelin-2 were the only significant predictor of the level of eGFR where they are the only significant predictor of the level of serum creatinine level. Serum Transgelin-2 level was higher in Stage III, but with no significant difference among the different ISS stages.

Woziwodzka et al. [18] detected between transgelin and serum creatinine (R = 0.29; p = 0.001), eGFR (CKD-EPICr) (R = −0.25; p = 0.007), uric acid (R = 0.19; p = 0.036), alanine (R = 0.18; p = 0.048) and aspartate (R = 0.26; p = 0.003) aminotransferases, ferritin (R = −0.22; p = 0.049), hepcidin (R = −0.25; p = 0.033), and urine cystatin C (R = 0.19; p = 0.042). Moreover, after exclusion of patients with smoldering MM, transgelin significantly correlated with serum FLC lambda (R = 0.18; p = 0.047) and serum periostin (R = −0.22; p = 0.013). In multiple

forward stepwise regression, uric acid was identified as the only independent predictor of serum transgelin (beta = 0.31; standard error = 0.13; p = 0.023).

However, baseline transgelin positively correlated with serum creatinine after follow-up (R = 0.37; p < 0.001) and negatively correlated with eGFR after follow-up (R = −0.33; p < 0.001). Moreover, higher baseline serum transgelin significantly predicted lower eGFR values after the follow-up period, independently of baseline eGFR, urinary concentrations of tubular injury markers (NGAL monomer and IGFBP-7), sex, age, and observation duration. Moreover, transgelin values in the upper tertile (i.e., above 110.6 ng/mL) were independently associated with lower eGFR at the end of observation [18].

Case studies on kidney biopsies in MM indicate a heterogenous spectrum of kidney lesions, with myeloma cast nephropathy (MCN) as the most common condition [35, 36].

Experimental evidence suggests that FLCs play a crucial role in the induction of pro-inflammatory and fibrotic changes within the kidney compartment [13, 14].

High levels of serum FLCs underlie this MM-specific lesion, which has translated into clinical utility of reducing FLCs and the corresponding renal recovery [37]. Data indicates that specific renal biopsy findings are also associated with prognosis in MM [38, 39].

Cast formation and interstitial fibrosis, as well as tubular atrophy (IFTA), have been adversely related to renal recovery in multivariate models including haematological status and clinical characteristics [39].

Histopathology characteristics (including IFTA) have been previously studied along with clinical variables in models predicting kidney failure. It has been emphasized that initial clinical appraisal does not correspond well to the underlying pathology, which highlights the importance of kidney biopsy and reliable biomarkers that could help to localize (e.g., proximal tubule injury, tubulointerstitial injury) and define the lesion. Identifying novel markers that could reflect developing nephropathology is of high interest, as it can facilitate early diagnosis

and may guide treatment choice. Ideally, development of non-invasive instruments, specific for distinct kidney lesions, could support treatment decisions and risk stratification in the future [40].

Limitations: Small sample size with single center study, Lack of research at this point, the study group is a heterogenous sample of patients from the outpatient clinic, and there are no standardized laboratory assays to measure transgelin concentrations. Also, transgelin-2 has been scarcely studied in MM and understanding of its mechanistic role and potential place as a marker of kidney injury requires differentiation of the major source of this molecule in circulation.

Conclusions:

While baseline characteristics, comorbidities, and most laboratory findings were similar between the case and control groups, several key differences emerged. Patients with MM displayed significantly lower serum M protein and creatinine, alongside lower total cholesterol but similar lipid profiles compared to controls. Interestingly, serum Transgelin-2 levels were significantly higher in the MM group and exhibited positive correlations with markers of liver function, blood sugar, kidney function, and uric acid, while demonstrating negative correlations with weight and estimated glomerular filtration rate (eGFR). Notably, Transgelin-2 emerged as a significant predictor of renal affection with promising sensitivity and specificity. Further analysis revealed that hemodialysis, hsCRP, serum creatinine, and Transgelin-2 were the only independent predictors of eGFR.

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