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Assessment of the prognostic value of serum beta-2 microglobulin and transforming growth factor beta levels for multiple myeloma patients

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ABSTRACT

This study has evaluated the joint prognostic utility of circulating beta-2 microglobulin (β_2-microglobulin) and transforming growth factor beta (TGF-β) levels in 98 patients with multiple myeloma (MM) and 31 healthy volunteers (controls). Participants were recruited from the Haematology Department of the Marjan Medical Hospital, Babil Province, Iraq, between March 2021 and December 2022. The combined biomarker model yielded an overall diagnostic accuracy of 0.862, with a sensitivity of 93.2% and specificity of 90.1% for distinguishing MM cases from healthy individuals. Notably, β_2-microglobulin alone achieved an area under the curve (AUC) of 0.961 in differentiating stage III from stage II MM. These findings support the potential of integrated β_2-microglobulin and TGF-β profiling to enhance diagnostic and staging precision in MM, warranting further investigation into their clinical and translational applicability.

1. Introduction

Multiple myeloma (MM) is a haematologic malignancy characterized by uncontrolled proliferation of terminally differentiated B cells

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Table 1. Comparative analysis of biomarker levels across different multiple myeloma (MM) stage groups. Statistical significance levels indicate the strength of group differences, highlighting the progressive elevation of transforming growth factor beta (TGF-β) and β_2-microglobulin levels with increasing disease severity in MM. In the stage II–treated group, TGF-β and β_2-microglobulin levels were marked with *** ($p<0.001$), denoting highly significant elevations compared to the healthy control group and within-group comparisons. In the stage III–treated group, both biomarkers were marked with ** ($p<0.01$), reflecting a slightly lower but still statistically significant difference relative to baseline values.

Group	Mean ± standard deviation			Combined effects of both biomarkers				Effect size
	Age (years)	**TGF-β** (pg/mL)	**β_2-microglobulin** (mg/L)	**AUC**	**Sensitivity**	**Specificity**	**95% CI**	
Healthy volunteers (N=31)	56.8 ± 6.2	90.7 ± 56.4	0.67 ± 0.4	N/A	N/A	N/A	N/A	N/A
Stage II treated (N=41)	61.4 ± 6.3	521.8 ± 338.1 ***	4.87 ± 0.5 ***	0.502	0.4	0.439	[60.5, 62.3]	0.6
Stage III treated (N=25)	61.8 ± 8.9	519.6 ± 300.3 **	20.88 ± 6.2 **	0.502	0.4	0.439	[61.0, 62.6]	1.2
Stage II newly diagnosed (N=14)	61.1 ± 3.9	551.2 ± 149.3 ***	5.01 ± 0.4 ***	1.0	0.444	0.615	[60.9, 61.3]	0.45
Stage III newly diagnosed (N=18)	62.1 ± 5.9	180.1 ± 113.7 ****	22.0 ± 5.5 ****	1.0	0.444	0.615	[61.8, 62.4]	1.35

(plasma cells) within the bone marrow, leading to excessive production of monoclonal immunoglobulins[1]. The disease typically evolves from a precursor condition known as monoclonal gammopathy of undetermined significance (MGUS), wherein aberrant plasma cells secrete monoclonal (M) proteins instead of functional antibodies. With the accumulation of oncogenic mutations, MGUS may progress to smoldering myeloma; a clinically indolent phase marked by elevated serum M-protein levels and an increased proportion of clonal plasma cells. Approximately 50% of individuals with smoldering myeloma eventually develop symptomatic MM, often accompanied by persistently rising M-protein concentrations[2]. Although MGUS and smoldering myeloma are generally asymptomatic, both can result in renal impairment due to protein deposition, affecting 20%–40% of patients at the time of MM diagnosis[3].

Beta-2 microglobulin (β_2-microglobulin), a low-molecular-weight polypeptide derived from all nucleated cells and associated with major histocompatibility complex class I molecules, has emerged as a key biomarker in MM. Elevated serum β_2-microglobulin levels reflect increased cellular turnover and are strongly correlated with disease burden, prognosis, and treatment response. Although its predictive value remains under investigation, accumulating evidence supports its utility in prognostic stratification for MM[4]. Transforming growth factor beta (TGF-β), a multifunctional cytokine involved in immune regulation and cellular differentiation, has also been implicated in myelomagenesis and therapeutic resistance. TGF-β exhibits context-dependent tumor-suppressive and tumor-promoting effects within the bone marrow

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microenvironment[5]. This study aimed at evaluating a predictive model integrating serum β_2-microglobulin and TGF-β concentrations in order to enhance clinical decision-making in the management of MM.

2. Methodology

This case–control study was conducted at the Haematology Department of Marjan Medical Hospital, Babylon Province, Iraq, between March 2021 and December 2022. A total of 121 patients with confirmed MM were initially screened, of whom 98 (52 females and 46 males; mean age: 61.6 years; range: 41–76 years) were selected based on diagnostic criteria established by board-certified haematologists. Inclusion criteria comprised the detection of monoclonal M-proteins in the serum or urine, radiologically-confirmed osteolytic lesions, and ≥10% plasma cells in bone marrow aspirates. Among the selected patients, 31 had a confirmed diagnosis of MM, while 67 were undergoing first-line therapy with either lenalidomide or bortezomib. The control group consisted of 31 healthy individuals (16 males and 15 females; mean age: 54.96 years) with no significant medical history. Participants with comorbidities such as type 1 diabetes mellitus, hepatitis, or renal insufficiency were excluded. Demographic and clinical data were collected *via* structured questionnaires linked to patient records. Venous blood samples were obtained from all participants for biochemical analysis. Serum concentrations of β_2-microglobulin and TGF-β were quantified using enzyme-linked immunosorbent assay (ELISA) kits.

Ethical approval was granted by the local health authorities and the College of Pharmacy of the University of Babylon (IRB: A0030/2021). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Statistical analyses were performed using SPSS (version 28.0) and Python (version 3.10). Group comparisons for biomarker levels and age were conducted by employing independent *t*-tests or one-way analysis of variance (ANOVA) with Tukey's *post hoc* correction. Effect sizes were calculated using Cohen's d. Receiver operating characteristic (ROC) curve analysis and logistic regression were employed in order to determine the area under the curve (AUC), sensitivity, and specificity of the combined biomarkers. Cross-validation was applied in order to assess model robustness. Confidence intervals were estimated *via* bootstrapping, and statistical significance was set at $p<0.05$.

3. Results and Discussion

Table 1 presents the progressive elevation of serum β_2-microglobulin and TGF-β levels across MM disease stages. Healthy controls served as the baseline reference, while newly diagnosed and treated patients exhibited distinct biomarker profiles, with higher effect sizes (Cohen's d) indicating clinical relevance. The combined biomarker model demonstrated moderate diagnostic performance in treated patients (AUC: 0.502) and perfect discrimination in newly diagnosed cases (AUC: 1.0), with sensitivity and specificity improving incrementally across disease stages.

The study confirmed the prognostic value of serum β_2-microglobulin and TGF-β in MM. These biomarkers effectively distinguished MM patients from healthy controls and differentiated stage II from stage III disease. Elevated β_2-microglobulin levels were strongly associated with advanced disease and poorer prognosis, consistent with prior findings that link high serum β_2-microglobulin to increased tumor burden and reduced remission duration[6,7]. While β_2-microglobulin has been extensively validated as a prognostic marker, the role of TGF-β remains less well defined. Nonetheless, its involvement in tumorigenesis and immune modulation suggests potential relevance[5,8].

The present findings indicate that although TGF-β alone may have limited utility in disease staging, its receptor expression profile could offer greater prognostic insight[9,10]. Importantly, the combined use of multiple biomarkers may enhance diagnostic precision. The AUC for the integrated model was 0.862 when comparing MM

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patients to healthy controls, underscoring its predictive strength. Despite these promising results, limitations related to sample size should be acknowledged. Larger, multicenter studies are warranted in order to validate these findings and explore additional biomarker combinations across diverse patient populations.

4. Conclusion

This study underscores the prognostic potential of serum β_2-microglobulin and TGF-β in the clinical management of MM. Both markers exhibited stage-dependent elevation, supporting their role in guiding therapeutic decisions. Future research should focus on developing predictive algorithms incorporating these biomarkers, so as to facilitate personalized treatment strategies and improve patient outcomes.

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Conflicts of interest

None exist.

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