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Long Non-coding RNA Morrbid is Upregulated in Multiple Myeloma Patients with Type 2 Diabetes

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Abstract: Background: Long non-coding RNAs are implicated in metabolic diseases and malignancies, but their role in multiple myeloma (MM) with type 2 diabetes mellitus (T2DM) remains unclear. This study evaluated Long non-coding RNA Morrbid expression in MM patients with/without T2DM. Methods: The study enrolled 107 MM patients (48 with T2DM, 59 without) and 72 non-MM controls (23 with T2DM, 49 without). Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples using red blood cell lysis. Total RNA was extracted from PBMCs, followed by reverse transcription, and the expression levels of Morrbid were detected by Reverse transcription-quantitative PCR. Results: We found that the expression of Morrbid was upregulated in the MM group compared to the non-MM patients. Within the MM group, the expression of Morrbid was significantly higher in patients with T2DM than in those without T2DM. In contrast, no significant difference in Morrbid expression was observed between T2DM and non-T2DM patients in the non-MM patients. Furthermore, we discovered a positive correlation between Morrbid expression and fasting blood sugar levels in MM patients. Operating characteristic curve analysis revealed an area under the curve of 0.822 (sensitivity 77.1%, specificity 79.7%) for diagnosing T2DM in MM, suggesting that Morrbid may serve as a novel diagnostic biomarker for T2DM in MM patients. Conclusions: The high expression of Morrbid in MM patients with T2DM may indicate its critical role in tumor-related glucose metabolism. Additionally, Morrbid may potentially serve as a diagnostic biomarker for T2DM in MM patients.

Keywords: Long non-coding RNA; LncRNA Morrbid; Multiple myeloma; Diabetes; Type-2 diabetes mellitus

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1. Introduction

Multiple myeloma (MM) is a malignant proliferative disorder of plasma cells, clinically characterized by anemia, renal impairment, hypercalcemia, and osteolytic bone lesions [1]. MM patients often experience rapid disease progression, and the disease exhibits a certain degree of genetic predisposition. In recent years, the incidence of MM has been increasing worldwide, making it the second most common malignancy in the hematopoietic system [2].

Globally, over 500,000 individuals are diagnosed with multiple myeloma annually, and this number continues to rise each year [3]. As MM progresses, patients are prone to developing a series of complications, which significantly impair their quality of life in advanced stages and impose a substantial burden on global healthcare systems. Metabolic alterations in MM cells are critical factors influencing disease prognosis and drug resistance. Among these changes, the glycolytic pathway plays a pivotal role in supporting the rapid proliferation and growth of MM cells [4]. MM cells adhere to the Warburg effect, enhancing aerobic glycolysis to meet their energy demands. Elevated glucose and lipid metabolism further provide additional energy sources to support the proliferation and growth of MM cells [5]. This metabolic reprogramming phenomenon is not only closely associated with the initiation and progression of tumors but also plays a significant role in other metabolic diseases. Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder, has seen its prevalence rise annually, becoming one of the most prominent global public health challenges. Notably, T2DM accounts for over 90% of all diabetes cases [6]. Notably, T2DM patients often exhibit dysregulated glucose and lipid metabolism, which shares certain similarities with the metabolic characteristics of MM cells. This suggests a potential link in their metabolic regulatory mechanisms. Further investigation into this connection may provide critical insights into the comorbidity mechanisms and the development of novel therapeutic strategies. A growing body of research indicates that genetic factors play a crucial role in the onset and progression of diseases. In particular, the dysregulation of long non-coding RNAs (lncRNAs) has been closely associated with various metabolic disorders [7–9].

LncRNAs are a class of non-protein-coding RNA molecules with specific nucleotide lengths. It is now widely accepted that lncRNAs play crucial roles in various biological processes, including cellular signal transduction, histone modification, protein translation, and the regulation of gene expression [10]. They play a pivotal role in processes such as glucose metabolism dysregulation, insulin resistance, and tumorigenesis. For instance, in T2DM certain lncRNAs have been found to regulate the expression of genes involved in insulin secretion and glucose metabolism [11–13]. In MM, lncRNAs can promote tumor cell proliferation and survival by modulating the Warburg effect and metabolic reprogramming [14]. Therefore, in-depth research into the regulatory mechanisms of lncRNAs in T2DM and MM will not only help elucidate the molecular basis of these two diseases but may also provide novel insights for developing combined therapeutic strategies targeting both metabolic disorders and tumors. LncRNA Morrbid, located on the F1 arm of human chromosome 2, is a long non-coding RNA that plays significant roles in various aspects of malignant tumors, including proliferation, migration, invasion, tumor immune microenvironment, and glucose-lipid metabolism [15–17]. Recent studies have demonstrated that Morrbid is involved in the regulation of glucose and lipid metabolism in both tumor cells and immune cells, particularly in glucose and lipid metabolic pathways. Moreover, transcriptomic analysis based on the TCGA database has revealed a significant association between Morrbid and glucose metabolism processes in various types of tumors [17]. Based on these findings, this study aims to investigate the expression levels of lncRNA Morrbid in MM patients with T2DM, MM patients without T2DM, T2DM patients without MM, and healthy controls. The results may provide insights into the mechanisms underlying glucose metabolism dysregulation in MM patients and could potentially contribute to the early detection of T2DM in this population.

2. Material and methods

2.1. Study population

This study has been approved by the Clinical Trial Ethics Committee of the Affiliated Hospital of Southwest

Medical University (Approval No.: KY2025090). We recruited 107 MM patients (48 with T2DM and 59 without T2DM) and 72 non-MM controls (23 with T2DM and 49 without T2DM) as controls. MM patients were primarily recruited from the Department of Hematology inpatient ward and the Multiple Myeloma Specialty Clinic at the Affiliated Hospital of Southwest Medical University. Non-MM controls were mainly selected from individuals undergoing routine health check-ups at the Physical Examination Center of the same hospital.

This study was divided into four groups: the MM with T2DM group (MM patients complicated by type 2 diabetes mellitus), the MM without T2DM group (MM patients without type 2 diabetes mellitus), the T2DM group (patients with type 2 diabetes mellitus only), and the healthy control group. The MM with T2DM group included patients who met the diagnostic criteria for MM according to the Chinese Guidelines for the Diagnosis and Treatment of Multiple Myeloma (2024 Revision) and simultaneously fulfilled the diagnostic criteria for T2DM as defined by the American Diabetes Association, additionally, patients were required to have a diabetes history of at least two years; Individuals with other types of diabetes (e.g., type 1 diabetes or secondary diabetes), hyperglycemia due to other identifiable causes, or concurrent malignancies were excluded. The MM without T2DM group included patients diagnosed with MM but without a history of T2DM, with fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels within the normal range (FPG < 7.0 mmol/L, HbA1c < 6.5%); Patients with any history of diabetes or abnormal glucose levels (FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5%) were excluded. The T2DM group included patients diagnosed with T2DM but without MM or other plasma cell disorders such as monoclonal gammopathy of undetermined significance (MGUS), plasma cell leukemia, Waldenström macroglobulinemia, or POEMS syndrome; Patients with a history of MM or other malignancies were excluded. The healthy control group included individuals without a history of MM or T2DM, with normal FPG and HbA1c levels, and without any first-degree relatives with a history of T2DM; Individuals with other metabolic disorders, malignancies, or abnormal glucose levels were excluded. All participants voluntarily enrolled in this study, and each individual provided written informed consent prior to participation.

The study primarily collected demographic characteristics of the study population through the medical records of the participants.

2.2. Sample preparation and RNA extraction from peripheral blood mononuclear cells

After an 8–10 hour overnight fast, approximately 3–5 mL of venous blood was drawn from the antecubital vein of each participant the following morning. Two tubes of blood samples were collected: one tube was sent to the Department of Laboratory Medicine at the Affiliated Hospital of Southwest Medical University for FBG level measurement using a glucose analyzer, while the other tube was transferred to the laboratory for sample processing and RNA extraction. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood using red blood cell lysis buffer. The PBMCs were then treated with Trizol, followed by the addition of chloroform and thorough mixing. After allowing the mixture to separate at room temperature, the upper aqueous phase was collected and mixed with pre-chilled isopropanol. The mixture was incubated at low temperature, after which the supernatant was discarded, and the pellet was washed with ethanol and centrifuged. Finally, the supernatant was removed, and the pellet was air-dried at room temperature before being resuspended in DEPC-treated water. The concentration and purity of RNA were measured using a NanoDrop spectrophotometer.

2.3. Detection of lncRNA Morrbid expression

Reverse transcription-quantitative PCR (RT-qPCR) was performed to detect lncRNA Morrbid expression. Total

RNA was reverse-transcribed into cDNA using a reverse transcription kit (Vazyme Biotech Co., Ltd.). Real-time PCR was conducted using SYBR Green (Vazyme Biotech Co., Ltd.) according to the manufacturer's instructions for reaction setup and cycling conditions. All reactions were performed on an ABI QuantStudio 5 Fast Real-Time PCR System. After PCR amplification, cycle threshold (CT) values were obtained, and data were analyzed using QuantStudio™ Design & Analysis Software. GAPDH was used as an internal control, and the relative expression of the target gene was calculated using the $2^{-\Delta CT}$ method. The qPCR analysis was performed using the following primer pairs: lncRNA Morrbid (Forward: 5′-ACCCCCAAGTCTCCTAACCA-3′; Reverse: 5′-GTTCAACCTCAGTGCCCAGT-3′) and GAPDH (Forward: 5′-ACCCAGAAGACTGTGGATGG-3′; Reverse: 5′-CACATTGGGGGTAGGAACAC-3′), which served as an internal control. All primers were designed using Primer-BLAST and verified for specificity.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 25.0 software. Normally distributed continuous data were expressed as mean ± standard deviation. The normality of sample data was assessed using the Kolmogorov-Smirnov test. Comparisons between two groups were conducted using the t-test or Mann-Whitney U test, and comparisons among multiple groups were performed using ANOVA or the chi-square test. Spearman correlation analysis was used to assess correlations. Logistic regression was employed to determine the causal relationship between lncRNA Morrbid expression and MM with T2DM. The diagnostic value of lncRNA Morrbid was evaluated using receiver operating characteristic (ROC) curve analysis, and its sensitivity and specificity were calculated. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of the four study groups

This study enrolled a total of 179 participants divided into four groups. No statistically significant differences were observed among the four groups in terms of gender, age, height, weight, or BMI ($P > 0.05$). Similarly, no significant differences were found between the two MM patient groups in lactate dehydrogenase (LDH) levels, β2-microglobulin levels, plasma cell percentage, or Durie-Salmon staging ($P > 0.05$). However, a significant difference in FBG levels was observed between the groups with and without diabetes (**Table 1).**

Table 1. Clinical characteristics of the four study groups

Parameters	MM with T2DM (*N* = 48)	MM without T2DM (*N* = 59)	T2DM (*N* = 23)	Healthy control (*N* = 49)	*P* value
Age (years)	63.04 ± 9.98	64.22 ± 9.42	62.04 ± 9.80	60.41 ± 7.76	0.191
Sex (male/female)	26/22	30/29	12/11	25/24	0.981
Weight (kg)	67.34 ± 7.73	67.03 ± 7.52	67.52 ± 8.02	66.58 ± 6.98	0.535
Height (cm)	168.63 ± 5.61	167.32 ± 5.52	167.54 ± 5.34	168 ± 6.12	0.453
BMI (kg/m^2)	24.89 ± 3.89	24.35 ± 3.35	24.92 ± 3.44	23.69 ± 3.64	0.759
LDH (U/L)	273.18 ± 203.53	237.44 ± 91.67	/	/	0.343
β2-MG (mg/L)	6.84 ± 6.75	6.22 ± 6.80	/	/	0.721
Ca^{2+} (mmol/L)	2.41 ± 0.28	2.42 ± 0.37	/	/	0.935

Table 1 (Continued)

Parameters	MM with T2DM (*N* = 48)	MM without T2DM (*N* = 59)	T2DM (*N* = 23)	Healthy control (*N* = 49)	*P* value
Cr (umol/L)	129.84 ± 122.56	161.22 ± 169.79	/	/	0.295
Plasma cells (%)	41.67 ± 24.20	32.01 ± 22.37	/	/	0.058
Durie-Salmon staging system					
I	20	25	/	/	0.905
II	18	20			
III	10	14			
FBG (mmol/L)	8.65 ± 1.92	5.42 ± 0.86	8.23 ± 2.35	5.13 ± 0.95	0.001**

*$P < 0.05$; **$P < 0.01$

3.2. Differences in the relative expression of lncRNA morrbid among the four study groups

The relative expression levels of lncRNA Morrbid in the four study groups are shown in **Table 2** and **Figure 1**, **Table 2** presents the relative expression levels of lncRNA Morrbid in the MM with T2DM group, MM without T2DM group, T2DM group, and healthy control group as 12.92 ± 13.40, 4.40 ± 6.85, 2.70 ± 2.53, and 1.64 ± 1.29, respectively. As illustrated in **Figure 1**, the relative expression of Morrbid was significantly higher in both MM groups (with and without T2DM) compared to the healthy control group ($P < 0.05$). Additionally, the expression of Morrbid was significantly higher in the MM with T2DM group than in the MM without T2DM group ($P < 0.01$). In contrast, no significant difference in Morrbid expression was observed between the T2DM group and the healthy control group.

Table 2. Relative expression levels of Morrbid in the four study groups

	MM with T2DM (*N* = 48)	MM without T2DM (*N* = 59)	T2DM (*N* = 23)	Healthy control (*N* = 49)	*P* value
Morrbid	12.92±13.40	4.40±6.85	2.70±2.53	1.64±1.29	0.001**

*$P < 0.05$; **$P < 0.01$

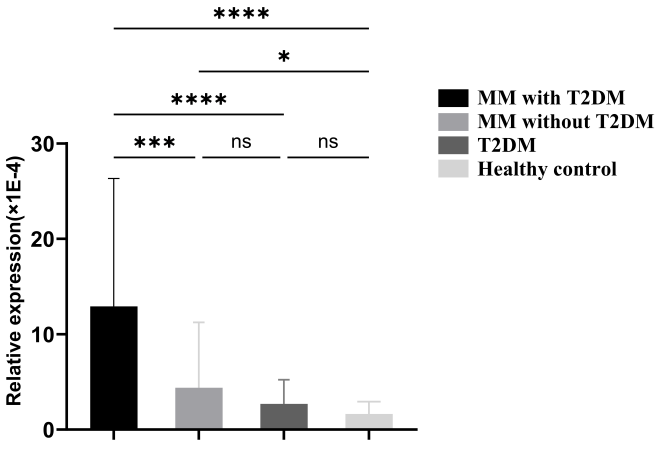

Figure 1. Differential expression of Morrbid among the four study groups.

Table 2. Relative expression levels of Morrbid in the four study groups

	MM with T2DM (*N* = 48)	MM without T2DM (*N* = 59)	T2DM (*N* = 23)	Healthy control (*N* = 49)	*P* value
Morrbid	12.92 ± 13.40	4.40 ± 6.85	2.70 ± 2.53	1.64 ± 1.29	0.001**

*$P < 0.05$; **$P < 0.01$

3.3. Correlation between the relative expression of lncRNA Morrbid and glucose-lipid metabolism indicators in MM patients

We aimed to determine whether the relative expression levels of Morrbid in MM patients were associated with biochemical parameters related to glucose-lipid metabolism. Pearson correlation analysis was performed to assess the relationship between the relative expression of Morrbid and glucose-lipid metabolism indicators in MM patients. The results (**Table 3**) showed that the expression of Morrbid was not significantly correlated with total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A (ApoA), apolipoprotein B (ApoB), fructosamine (FMN), TG/HDL ratio, or ApoB/ApoA ratio ($P > 0.05$). However, a positive correlation was observed between Morrbid expression and FBG ($r = 0.351$, $P < 0.05$). Furthermore, linear regression analysis was conducted to quantify the impact of Morrbid expression on FBG levels in MM patients. The results indicated that Morrbid expression was positively correlated with FBG, with each unit increase in Morrbid expression associated with an approximate 0.122 mmol/L increase in FBG levels (**Figure 2**).

Table 3. Correlation analysis between Morrbid and glucose-lipid parameters

Parameters	r	*P* value
TC	-0.056	0.656
TG	0.063	0.604
HDL	-0.004	0.978
LDL	-0.062	0.623
ApoA	-0.014	0.908
ApoB	-0.099	0.43
FMN	0.009	0.948
TG/HDL	0.066	0.597
ApoB/ApoA	-0.076	0.542
FBG	0.351	0.001**

*$P < 0.05$; **$P < 0.01$

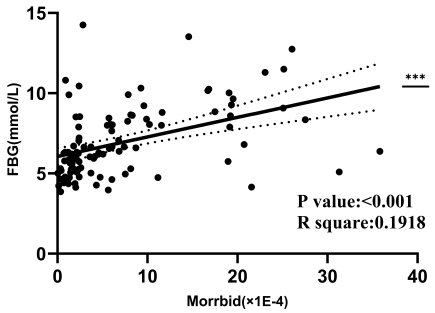

Figure 2. Linear regression analysis of Morrbid relative expression vs. FBS levels.

3.4. Correlation between lncRNA Morrbid and the risk of developing T2DM in MM patients

Logistic regression was performed to estimate the relationship between the relative expression levels of Morrbid and the risk of developing T2DM in MM patients, calculating the odds ratios (ORs) and 95% confidence intervals (CIs) for Morrbid. The logistic regression analysis revealed that for each unit increase in the relative expression of Morrbid, the risk of developing T2DM in MM patients increased by approximately 13.5% (**Table 4**).

Table 4. Logistic regression analysis

	P value	OR	95% CI	
			Lower	Upper
Morrbid	0.001**	1.135	1.060	1.215

*$P < 0.05$; **$P < 0.01$

3.5. Diagnostic potential of lncRNA Morrbid

To evaluate the diagnostic potential of Morrbid for T2DM in MM patients, we constructed a ROC curve for Morrbid and calculated the area under the curve (AUC) (**Figure 3**). The AUC value for lncRNA Morrbid was 0.822. **Table 5** presents the optimal cutoff value, sensitivity, and specificity of Morrbid based on the ROC analysis. Overall, lncRNA Morrbid exhibited a high AUC value ($P < 0.01$), suggesting its potential as a diagnostic biomarker for T2DM in MM patients.

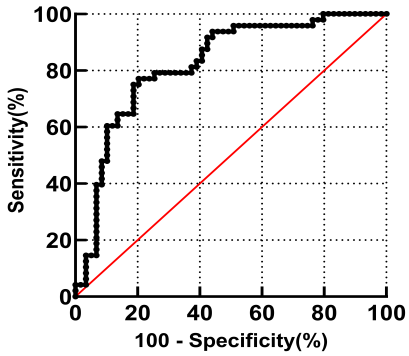

Figure 3. ROC curve of Morrbid.

Table 5. Receiver Operating Characteristic (ROC) curve

	Morrbid
AUC	0.822
SE	0.041
P value	0.0001
95% CI	0.742 ~ 0.903
Sensitivity	0.771
Specificity	0.797
Youden index	0.567
Cut-off	5.051

4. Discussion

With the rising global incidence of MM, this disease has garnered increasing attention [18]. As one of the most significant chronic diseases worldwide, T2DM has a vast patient population that overlaps with MM patients. T2DM, through the overactivation of insulin-related signaling pathways [19], can further accelerate the proliferation of MM tumor cells, thereby influencing disease progression [20]. In current research on these two diseases, genetic factors are considered key contributors to their pathogenesis, with lncRNAs playing a crucial role [21–24]. Investigating the potential roles of lncRNAs in the comorbidity of MM and T2DM may provide critical insights into the underlying mechanisms of their co-occurrence and the development of novel therapeutic strategies.

This study is the first to investigate the expression levels and clinical significance of lncRNA Morrbid in patients with MM complicated by T2DM. In our preliminary investigation with a limited sample size, we observed significant differences in the relative expression of lncRNA Morrbid between MM and non-MM populations. Considering previously published research and the potential roles of lncRNAs in various malignant diseases, we aimed to determine whether lncRNA Morrbid plays a critical role in glucose and lipid metabolism in tumor cells. To this end, we collected clinical data and analyzed the impact of lncRNA Morrbid on hematopoietic capacity, glucose-lipid metabolism, tumor burden, and immune reserves in MM patients. Ultimately, our preliminary findings suggest a potential association between lncRNA Morrbid expression levels and glucose metabolism dysregulation in MM patients, however, this observed relationship requires further validation through larger-scale studies to establish its clinical significance. Therefore, we further collected data from four study groups based on the presence of T2DM and MM, and measured the relative expression levels of lncRNA Morrbid for detailed analysis.

Notably, unlike most previous studies on lncRNA expression profiles, this study utilized PBMCs to measure Morrbid expression. PBMCs, a critical cell population isolated from blood, include monocytes, their derived macrophages, and lymphocytes. These cells cover approximately 80% of the coding gene expression in the human genome. In the study by Jonathan J. Kotzin et al., lncRNA Morrbid was shown to be highly and specifically expressed in mature eosinophils, neutrophils, and monocytes in both mice and humans, making it a minimally invasive and easily accessible biomarker for clinical research [25]. PBMCs can reflect the gene expression characteristics of multiple organs without relying on invasive techniques. Currently, PBMCs have been widely used in gene expression analysis for various diseases [26,27]. Based on these reasons, we chose to collect PBMCs from participants to detect Morrbid expression.

Our study found that the expression of lncRNA Morrbid was significantly higher in MM patients with T2DM compared to MM patients without T2DM and healthy controls ($P < 0.01$). This result show partial consistency with the findings reported by Baiden et al., suggesting that while Morrbid is frequently overexpressed in malignant tumors, its potential role in the interplay between tumorigenesis and metabolic disorders requires more substantial evidence [28]. We cautiously speculate that elevated Morrbid expression might influence cancer cell glucose metabolism through GLUT-1 regulation, though the exact mechanisms demand rigorous experimental verification. Previous studies have shown that lncRNAs can promote rapid tumor cell proliferation by modulating the Warburg effect and metabolic reprogramming [29,30]. Our study also provides preliminary evidence suggesting Morrbid's potential involvement in metabolic reprogramming, which may contribute to its regulatory role in glucose metabolism that could subsequently promote MM cell proliferation and T2DM development. However, these observations require further experimental validation to establish definitive mechanistic links. Additionally, it is noteworthy that the expression of Morrbid only showed significant differences between MM patients with

and without T2DM, while no such differences were observed in non-MM populations (i.e., T2DM patients vs. healthy individuals). This suggests that Morrbid may undergo metabolic reprogramming specifically under the mutual influence of MM and T2DM comorbidity. However, the specific pathways and mechanisms through which Morrbid exerts its effects require further investigation.

Using Pearson correlation analysis, we found that the expression of lncRNA Morrbid was positively correlated with FBG ($r = 0.351$, $P < 0.01$). However, no significant correlations were observed between Morrbid expression and other glucose-lipid metabolism indicators, such as TC, TG, HDL, LDL. These results suggest that Morrbid may primarily influence glucose metabolism dysregulation in MM patients through glucose metabolic pathways. Further linear regression analysis revealed that each unit increase in the relative expression of Morrbid was associated with an approximate 0.122 mmol/L increase in FBG levels, further confirming the critical role of Morrbid in glucose metabolism.

HbA1c, as a reliable diagnostic indicator for diabetes second only to the gold standard oral glucose tolerance test (OGTT), has been widely recognized for its accessibility and diagnostic accuracy, and its use is firmly established in current clinical guidelines for diabetes management. However, for populations with malignancies such as MM, lncRNAs offer significant advantages for early diabetes detection due to their resistance to interference from factors such as shortened red blood cell lifespan or chemotherapy. To evaluate the diagnostic potential of lncRNA Morrbid for T2DM in MM patients, we constructed a ROC curve and calculated the AUC. The results showed that the AUC value for Morrbid was 0.822 ($P < 0.01$), indicating high considerable accuracy. Additionally, Morrbid exhibited a sensitivity of 0.771 and a specificity of 0.797, further supporting its potential as a diagnostic biomarker. These collective findings suggest that Morrbid may represent a potential candidate biomarker for T2DM detection in MM populations, though further validation studies are warranted.

5. Conclusion

In summary, our study observed elevated expression of lncRNA Morrbid in MM patients with T2DM compared to those with MM alone and healthy controls. The identified association between Morrbid expression and glucose metabolism dysregulation in MM patients suggests its possible involvement in the MM-T2DM comorbidity mechanism, though this requires further investigation. These preliminary findings indicate that Morrbid may represent a potential candidate biomarker for T2DM detection in MM populations, pending validation in larger, multi-center studies.However, this study has several limitations that should be acknowledged.

First, as a single-center study with a relatively small sample size, our findings may not fully capture the expression patterns of Morrbid across diverse ethnic populations and geographic regions. Second, this study did not account for potential variations in treatment regimens between MM and T2DM patients, precluding assessment of therapeutic interventions on the Morrbid associations. Potential interactions between antimyeloma therapies and glucose-lowering agents were not systematically evaluated, which could confound the metabolic observations. Furthermore, this study did not perform detailed stratification based on the temporal sequence of MM and T2DM onset, consequently precluding analysis of potential causal relationships between disease development and Morrbid expression patterns. Additionally, the study was restricted to expression profiling without functional validation through in vitro/vivo models, leaving the mechanistic basis of Morrbid's metabolic regulation unresolved. Finally, the cross-sectional design precludes longitudinal assessment of Morrbid expression dynamics during disease progression or therapy and prevents continuous glucose monitoring-based metabolic characterization in T2DM

patients. These outstanding issues necessitate comprehensive follow-up studies incorporating multi-ethnic cohorts, large-scale samples, and multi-omics approaches to ultimately enhance precision assessment capabilities for comorbid patients and advance medical progress in both multiple myeloma and diabetes research.

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Disclosure statement

The authors declare no conflict of interest.

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