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Original Article

Clinical outcomes of lenalidomide, bortezomib, and dexamethasone in multiple myeloma patients

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Abstract: Objective: To investigate the clinical benefits of the combination therapy involving lenalidomide, bortezomib, and dexamethasone in treating multiple myeloma (MM). Methods: This retrospective analysis included 182 patients with MM treated between January 2022 and June 2025. The patients were divided into a Lenalidomide group (n=93) and a control group (n=89). Before and after treatment, lactate dehydrogenase (LDH), β_2-microglobulin, monoclonal protein, myeloma cells, serum calcium (CA), hemoglobin (Hb), free light chain (FLC), serum creatinine (Scr), Blood urea nitrogen (BUN), and Visual Analogue Scale (VAS) were compared between the groups. Adverse reactions were also recorded and compared. A nomogram model was established and evaluated using RStudio. Results: The Lenalidomide group showed a significantly better therapeutic response than the control group (P<0.05). The β_2-microglobulin, monoclonal protein, myeloma cells, CA, FLC-κ, FLC-λ, Scr and BUN in the nalidomide group were lower than those in the control group (all P<0.05). Conversely, Hb and LDH levels were higher among patients receiving lenalidomide (both P<0.05). After treatment, the VAS score in the lenalidomide group was lower than that in the control group (P<0.05). The results of the receiver operating characteristic curve showed that the area under curve was 0.942 [95% CI (0.907-0.977)]. The actual curve predicted by the nomogram model is similar to the ideal curve. Conclusion: Lenalidomide, bortezomib, and dexamethasone, demonstrate significant clinical efficacy in treating multiple myeloma.

Keywords: Multiple myeloma, bortezomib, dexamethasone, lenalidomide, curative effect

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by clinical manifestations such as bone pain, hypercalcemia, anaemia, and renal impairment [1]. The incidence of this condition has been steadily increasing, particularly among middle-aged and older adults. Without prompt and effective treatment, complications like renal failure and recurrent infections can worsen the prognosis, posing a significant threat to patient survival and quality of life [2]. In recent years, the advent of novel agents, including the proteasome inhibitor bortezomib and the immunomodulatory drug lenalidomide, has significantly transformed the treatment landscape for MM. This has led to improved clinical outcomes and notably extended median survival. Bortezomib induces tumor cell apoptosis by suppressing proteasome activity [3, 4], while lenalidomide, a second-generation immunomodulatory agent, exerts potent anti-tumor effects through immune regulation and anti-angiogenesis. Dexamethasone, a corticosteroid, is directly cytotoxic to myeloma cells and acts synergistically with other agents [5]. Bortezomib and lenalidomide possess distinct yet complementary anti-myeloma mechanisms and can both enhance the therapeutic activity of dexamethasone. While the combination of these three drugs is a well-established regimen, further research is needed to fully understand its specific effects on the inflammatory response and immune function in patients [6]. Therefore, this study was designed to evaluate the efficacy and safety of the bortezomib, dexamethasone, and lenalidomide combination therapy on these specific parameters in patients with MM, aiming to provide a deeper insight into its clinical application.

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Materials and methods

Calculation of sample size

Based on the pre-test data (Efficient of 90% in the lenalidomide group and 70% in the control group), the following formula was used:

$$N = \frac{\left[Z_{1-\frac{\alpha}{2}}\sqrt{2\bar{p}\bar{q}} + Z_{1-\beta}\sqrt{p_1q_1+p_2q_2}\right]^2[(1+(n-1)\rho)]}{n(p_1-p_2)^2}$$

Set α=0.15, 1-β=0.90, and 96 cases are needed for calculation. Considering the 20% shedding rate, at least 116 cases need to be included.

Subjects

A total of 182 patients with MM admitted to Chengdu First People's Hospital from January 2022 to June 2025 were enrolled in this retrospective study. They were assigned to two groups according to treatment plans: the lenalidomide group (n=93) and the control group (n=89).

Inclusion criteria: (1) MM diagnosed by pathological examination, with no other blood system diseases. (2) No diseases related to the immune system.

Exclusion criteria: (1) With severe liver and kidney dysfunction or other organ dysfunction. (2) Expected survival time <6 courses or unable to complete at least 6 courses of treatment. (3) With mental disorders or kidney disease caused by hypertension or diabetes.

This study was approved by the Ethics Committee of Chengdu First People's Hospital. The technical roadmap of this study is illustrated in **Figure 1**.

Treatment methods

The control group consisted of patients treated with bortezomib (No. 936210101, Shiyao Group Ouyi Pharmaceutical Co., Ltd.) and dexamethasone (No. 1805252111, Chenxin Pharmaceutical Co., Ltd.). Bortezomib was administered at 1.3 mg/m^2 via subcutaneous injection, either twice weekly or once weekly, for a total of four doses. Dexamethasone (20 mg) was administered orally or intravenously, concurrently with bortezomib, for two consecutive days. Each treatment cycle lasted 28 days, with at least two cycles. Dose adjustments, such as extending the bortezomib dosing interval or reducing the dexamethasone dose, were noted in some elderly patients, particularly those experiencing concurrent infection or severe adverse reactions.

The lenalidomide group received lenalidomide (No. 20180801, Beijing Shuanglu Pharmaceutical Co., Ltd.) alongside the regimen for the control group. Lenalidomide was administered orally at 10-25 mg/day for 14-21 days continuously, with each cycle lasting 28 days and a minimum of two cycles.

The dosage and frequency of medication in the above plan were determined based on the treatment experience of Chengdu First People's Hospital.

Observed indexes

(1) The clinical efficacy in both groups was assessed in accordance with the International Myeloma Working Group criteria. Complete remission (CR) was defined as the disappearance of M protein in serum and urine, confirmed by negative serum and urine immunofixation electrophoresis. Stringent complete remission (sCR) required CR criteria plus bone marrow findings (smear, flow cytometry, and biopsy), showing only non-clonal plasma cells. Very good partial remission (VGPR) was defined by the absence of serum M protein but positive results in immunofixation electrophoresis. Partial remission (PR) was defined as at least a 90% reduction in 24-hour urinary M protein, while minimal remission (MR) was a 25-49% decrease in serum M protein. Stable disease (SD) was a failure to meet the above criteria, and progression disease (PD) was a 25% increase in serum M protein. The total clinical effective rate was calculated as 1 - (SD + PD cases)/total study cases × 100%.

(2) Biochemical indicators: Lactate dehydrogenase (LDH) levels in the two groups were detected by the rate method. Immunofixation electrophoresis was used to determine the proportion of β_2-microglobulin, monoclonal protein, and myeloma cells before and after treatment. Free light chain (FLC) was measured by immunoturbidimetry. Haemoglobin (Hb), serum creatinine (Scr) and blood urea nitrogen (BUN) were detected by colourimetry.

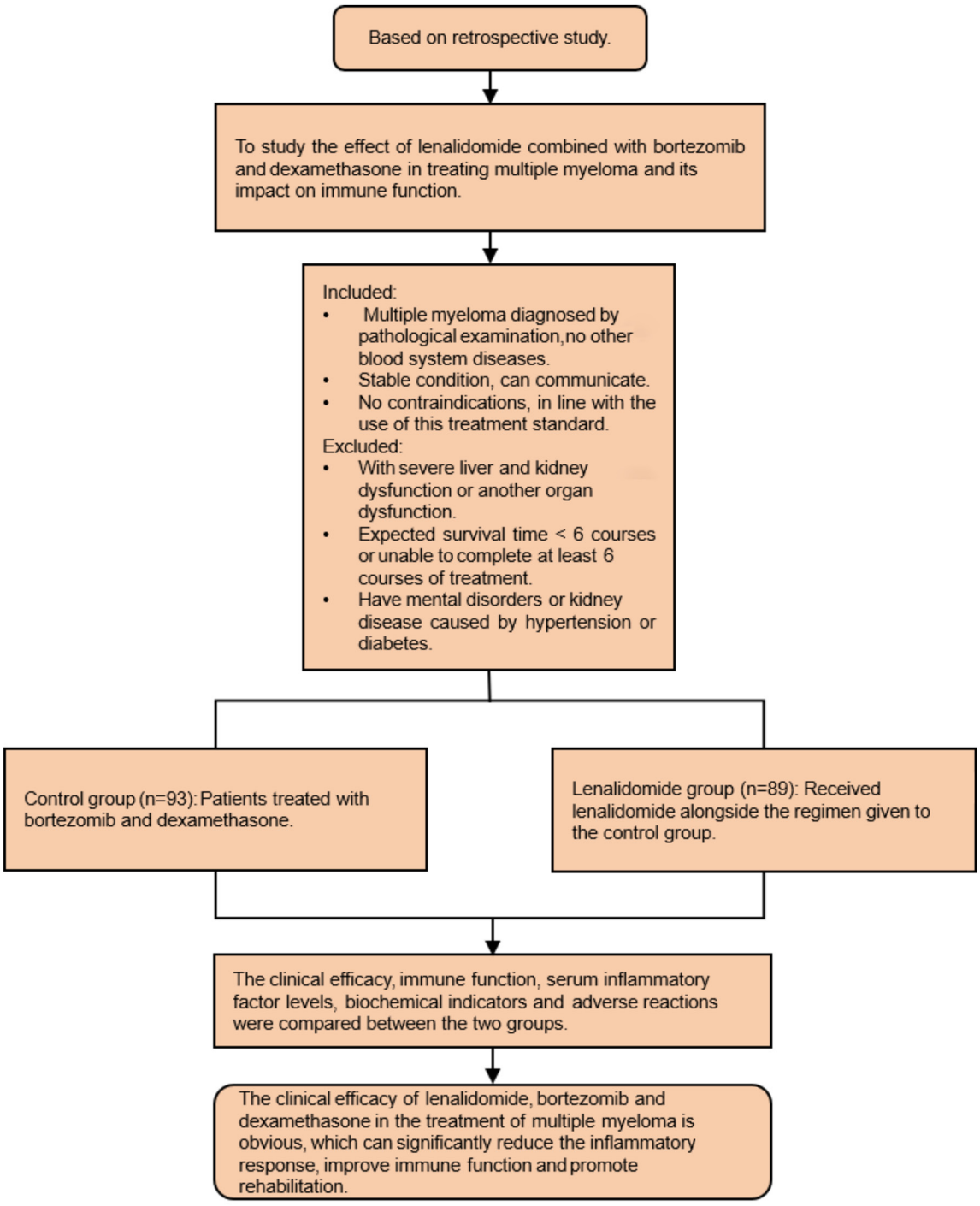

Figure 1. Technology roadmap.

(3) Pain intensity was measured via the visual analogue scale (VAS) before and after surgery. Higher scores correlated with worsened pain.

(4) Adverse reactions: Adverse events were evaluated and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Statistical methods

The statistical analysis was performed with SPSS 23.0 software. Measurement data was presented as mean ± standard deviation ($\bar{x}\pm sd$), and comparisons were made through t-tests. As for count data, it was displayed as case numbers or percentages, with chi-square

Table 1. Comparison of baseline information

Clinical Features	Lenalidomide group (n=93)	Control group (n=89)	χ^2/t	*P*
Age	52.51±10.18	53.49±11.07	-0.628	0.531
Sex			0.424	0.515
Male	52 (55.91)	54 (60.67)		
Female	41 (44.09)	35 (39.33)		
ISS			1.823	0.402
I	38 (40.86)	45 (50.56)		
II	27 (29.03)	23 (25.84)		
III	28 (30.11)	21 (23.60)		
High-risk cytogenetics			0.103	0.748
Yes	26 (27.96)	23 (25.84)		
No	67 (72.04)	66 (74.16)		
ECOG ≥2 points			1.757	0.185
Yes	24 (25.81)	31 (34.83)		
No	69 (74.19)	58 (65.17)		
Hypercalcemia			2.116	0.146
Yes	1 (1.08)	4 (4.49)		
No	92 (98.92)	85 (95.51)		
Anemia			2.596	0.107
Yes	37 (39.78)	46 (51.69)		
No	56 (60.22)	43 (48.31)		
Bone damage			0.277	0.599
Yes	78 (83.87)	72 (80.90)		
No	15 (16.13)	17 (19.10)		

ISS: International Staging System; ECGO: Eastern Cooperative Oncology Group.

tests employed for comparisons. Multivariate logistic regression analysis was performed to assess the correlation between each index and treatment efficacy, followed by the construction of a nomogram model. Its clinical utility was evaluated using receiver operating characteristic (ROC) curves, area under the curve (AUC), decision curve analysis (DCA) and Hosmer-Lemeshow (HL) test. A *P*-value less than 0.05 was deemed to indicate statistical significance.

Results

Comparison of baseline data

The patients had an average age of 52.99±10.60 years, with 26.78% being ISS stage III. In the cytogenetic examination, 49 patients (26.78%) were high-risk, and 133 (72.68%) were standard-risk. There were no significant differences in terms of baseline data (P_{age}=0.531, P_{sex}=0.515, P_{ISS}=0.402, $P_{High\text{-}risk\ cytogenetics}$=0.748, $P_{ECOG\geq2}$=0.185, $P_{Hypercalcemia}$=0.146, P_{Anemia}=0.107, $P_{Bone\ damage}$=0.599) (**Table 1**).

Comparison of clinical efficacy

After treatment, the lenalidomide group exhibited a superior overall efficacy rate compared to the control group (*P*=0.02). In the control group, there were 13 cases of sCR, 7 cases of CR, 9 cases of VGPR, 24 cases of PR, 17 cases of MR and 19 cases of SD + PD. In the lenalidomide group, there were 29 cases of sCR, 10 cases of CR, 14 cases of VGPR, 19 cases of PR, 15 cases of MR, and 6 cases of SD + PD. See **Figure 2**.

Pre-intervention biochemical parameters were equivalent between the groups ($P_{\beta2\text{-microglobulin}}$=0.752; $P_{monoclonal\ protein}$=0.738; $P_{Myeloma}$=0.477; P_{LDH}=0.876; P_{CA}=0.852; P_{Hb}=0.378). Post-treatment analysis revealed decreased β_2-microglobulin (3.87±0.13 μg/mL), monoclonal protein (23.61±3.25 g/L), myeloma cell counts (13.98±2.14%) and CA (1.64±0.33

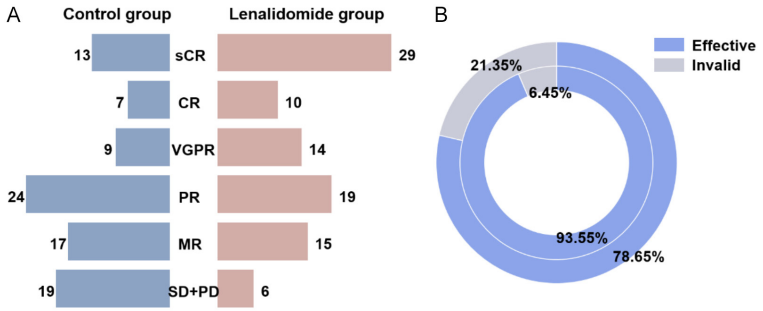

Figure 2. Comparison of clinical efficacy between the two groups. A. The comparison of each curative effect index; B. The total effective rate comparison, in which the outer ring is the control group and the inner ring is the lenalidomide group. sCR: strict complete remission; CR: complete remission; VGPR: very good partial remission; PR: partial remission; MR: minimal remission; SD: stable disease; PD: disease progression; OR: clinical total effective rate.

mmol/L) in the lenalidomide group, differing notably from the control (6.48±0.33 μg/mL; 28.94±3.42 g/L; 17.35±2.69%; 2.01±0.57 mmol/L) ($P_{\beta 2\text{-microglobulin}}$<0.001; $P_{\text{monoclonal protein}}$<0.001; P_{Myeloma}<0.001; P_{CA}<0.001). Conversely, levels of LDH (385.26±26.33 U/L) and Hb (125.06±13.84 mmol/L) were higher in patients with lenalidomide (control group: 214.65±22.47 U/L; 93.18±11.46 mmol/L) (P_{LDH}<0.001; P_{Hb}<0.001). See **Figure 3**.

There were no differences in FLC-κ and FLC-λ between the two groups before treatment ($P_{uFLC-\kappa}$=0.330; $P_{uFLC-\lambda}$=0.820; $P_{sFLC-\kappa}$=0.310; $P_{sFLC-\lambda}$=0.653). The therapeutic intervention resulted in significant decreases in both biomarkers for all patients, with the lenalidomide-treated (uFLC-κ: 16.28±1.33 mg/L; uFLC-λ: 45.05±2.76 mg/L; sFLC-κ: 59.36±13.51 mg/L; sFLC-λ: 74.28±16.44 mg/L) subjects showing more pronounced reductions than control counterparts ($P_{uFLC-\kappa}$<0.001; $P_{uFLC-\lambda}$<0.001; $P_{sFLC-\kappa}$<0.001; $P_{sFLC-\lambda}$<0.001). See **Table 2**.

Post-treatment analysis revealed significantly lower renal function markers in the nalidomide group (Scr: 116.35±13.63 μmol/L; BUN: 5.19±0.64 mmol/L) compared to controls (Scr: 138.32±15.32 μmol/L; BUN: 6.84±0.73 mmol/L) (P_{Scr}<0.001; P_{Scr}<0.001; **Table 3**).

Comparison of VAS scores

While initial VAS measurements weren't comparable between the two groups (P=0.853), therapeutic intervention yielded two key findings: (1) both cohorts exhibited decreased pain scores relative to baseline, and (2) the lenalidomide group achieved significantly lower scores than the control group (P<0.001, **Table 4**).

Comparison of adverse reactions

Constipation, diarrhoea and intestinal obstruction were the main gastrointestinal symptoms. When juxtaposed against the lenalidomide group, the control cohort exhibited a heightened prevalence of diarrhoea (P=0.15). Infections mainly involved the upper respiratory tract and lungs ($P_{\text{upper respiratory tract}}$=0.606; P_{lungs}=0.888). Variations across groups were also noted in thrombocytopenia, neutropenia, anaemia, limb oedema, and fever ($P_{\text{thrombocytopenia}}$<0.001; $P_{\text{neutropenia}}$=0.008; P_{anaemia}=0.001; $P_{\text{limb oedema}}$<0.001; P_{fever}=0.008, **Table 5**).

Construction and evaluation of a nomogram

The study incorporated multiple immune-related markers (LDH, β_2-microglobulin, monoclonal protein, myeloma cells, uFLC-κ, uFLC-λ, sFLC-κ, and sFLC-λ), which exhibited significant variations between the groups. Indicators with significant differences were included. Initial multicollinearity screening revealed that LDH and β_2-microglobulin had a variance inflation factor (VIF) exceeding the threshold (VIF_{LDH}=10.555, $VIF_{\beta 2\text{-microglobulin}}$=11.998), confirming their collinearity with other predictors. Consequently, the variable was excluded, and the final logistic regression model was derived using the remaining significant predictors (**Table 6**). Based on the regression coefficients, a nomogram was developed using R software (**Figure 4**). The model's predictive performance was evaluated via ROC analysis, with an AUC of 0.942 [95% CI (0.907-0.977)]. The HL test calculation showed that P=0.059. Further validation through calibration curves indicated strong agreement between predicted and observed outcomes, supporting the model's clinical utility (**Figure 5**).

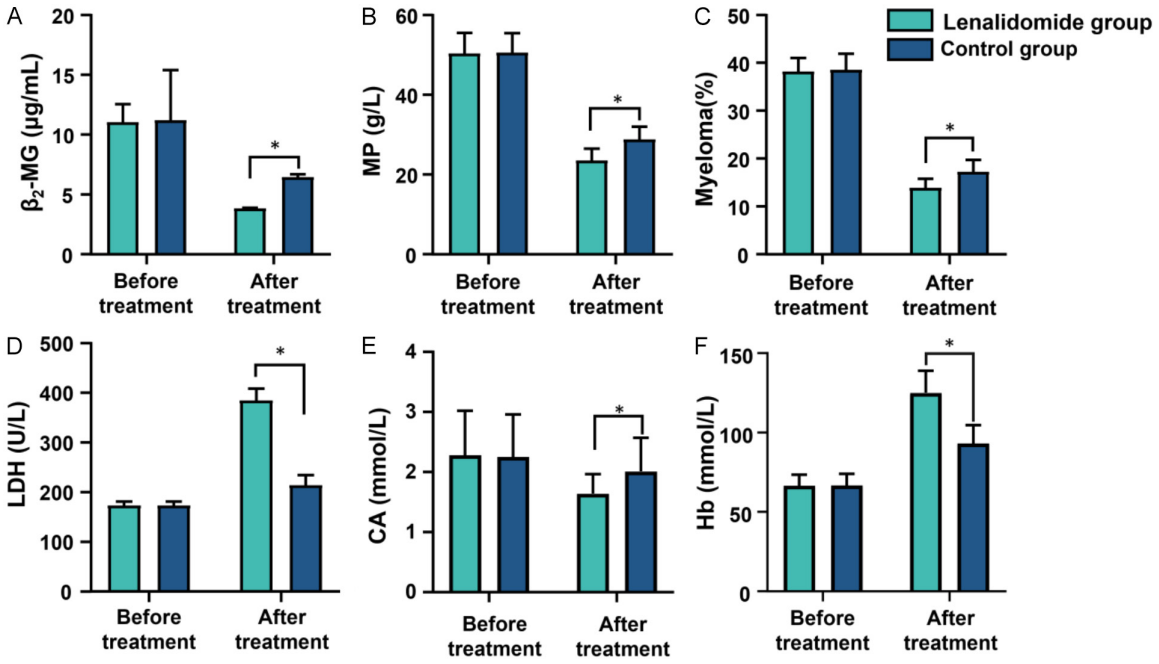

Figure 3. Comparison of biochemical indexes between the two groups before and after treatment. A. The comparison of β_2-MG levels between the two groups before and after treatment; B. The comparison of MP levels between the two groups before and after treatment; C. The comparison of Myeloma levels between the two groups before and after treatment; D. The comparison of LDH levels between the two groups before and after treatment; E. The comparison of CA levels between the two groups before and after treatment; F. The comparison of Hb levels between the two groups before and after treatment. β_2-MG: β_2-microglobulin; MP: monoclonal protein; LDH: lactate dehydrogenase; CA: serum calcium; Hb: hemoglobin. * indicates $P<0.05$ for comparison between two groups.

Table 2. Comparison of FLC-κ and FLC-λ ($\bar{x}\pm sd$, mg/L)

Index	Lenalidomide group (n=93)	Control group (n=89)	*t*	*P*
uFLC-κ				
Before treatment	20.19±2.36	20.54±2.47	-0.978	0.330
After treatment	16.28±1.33*	18.74±1.59	-11.297	<0.001
uFLC-λ				
Before treatment	56.78±4.14	56.92±4.72	-0.228	0.820
After treatment	45.05±2.76*	50.43±3.12	-12.335	<0.001
sFLC-κ				
Before treatment	279.61±15.14	277.24±16.39	1.018	0.310
After treatment	59.36±13.51*	74.39±11.45	-8.071	<0.001
sFLC-λ				
Before treatment	328.36±12.17	329.39±18.45	-0.451	0.653
After treatment	74.28±16.44*	102.21±13.83	-12.376	<0.001

uFLC: urinary free light chains; sFLC: serum free light chains. Compared with the control group, *P<0.05.

Discussion

MM is a malignancy of plasma cells within the bone marrow, characterized by the abnormal proliferation of plasma cells and the excessive production of monoclonal immunoglobulin or light chains (M protein). This process results in tissue and organ damage [7, 8]. Without treatment, the median survival is typically 6 to 12 months. Consequently, clinical treatment focuses on prolonging survival, managing symptoms, and improving quality of life. Most MM

Table 3. Comparison of renal function indexes

Index	Lenalidomide group (n=93)	Control group (n=89)	*t*	*P*
Scr (μmol/L)				
Before treatment	231.27±22.16	232.48±22.17	-0.365	0.715
After treatment	116.35±13.63*	138.32±15.32	-10.232	<0.001
BUN (mmol/L)				
Before treatment	8.43±1.27	8.24±1.35	1.029	0.305
After treatment	5.19±0.63*	6.84±0.73	-16.448	<0.001

Scr: serum creatinine; BUN: blood urea nitrogen. Compared with the control group, *P<0.05.

Table 4. Comparison of VAS scores ($\bar{x}$±sd, point)

Index	Lenalidomide group (n=93)	Control group (n=89)	*t*	*P*
Before treatment	7.63±1.32	7.67±1.56	-0.186	0.853
After treatment	3.05±0.67	5.44±1.19	-16.813	<0.001

VAS: Visual Analogue Scale.

Table 5. Comparison of adverse reactions during treatment (cases, %)

Adverse events	Lenalidomide group (n=93)	Control group (n=89)	χ^2	*P*
Gastrointestinal symptoms				
Constipation	29 (31.18)	26 (29.21)	0.084	0.772
Diarrhea	11 (11.83)	23 (25.84)	5.880	0.015
Intestinal obstruction	2 (2.15)	3 (3.37)	0.255	0.614
Infection				
The upper respiratory tract	19 (20.43)	21 (23.60)	0.266	0.606
Lungs	10 (10.75)	9 (10.11)	0.020	0.888
Others	6 (6.45)	2 (2.25)	2.005	0.157
Thrombocytopenia	57 (61.29)	79 (88.76)	18.175	<0.001
Neutropenia	32 (34.41)	48 (53.93)	7.037	0.008
Anemia	12 (12.90)	29 (32.58)	10.093	0.001
Peripheral neuritis	45 (48.39)	54 (60.67)	2.768	0.096
Limb oedema	3 (3.23)	17 (19.10)	12.734	<0.001
Fever	4 (4.30)	14 (15.73)	6.993	0.008

Table 6. Multiple logistic regression

Index	*B*	*SE*	*Wald*	*P*	*OR*	*95% CI*
MP	0.322	0.102	10.045	0.002	1.380	1.131-1.684
Myeloma	-0.391	0.140	7.744	0.005	0.677	0.514-0.891
uFLC-k	-0.574	0.199	8.292	0.004	0.563	0.381-0.832
uFLC-λ	-0.489	0.133	13.533	<0.001	0.613	0.472-0.796
sFLC-k	0.019	0.024	0.629	0.428	1.019	0.972-1.069
sFLC-λ	0.016	0.019	0.674	0.412	1.016	0.978-1.055

MP: monoclonal protein; FLC: Free Light Chain; uFLC: urinary free light chains; sFLC: serum free light chains.

patients present with the "CRAB" features: hypercalcemia (C), renal failure (R), anaemia (A), and bone disease (B) [9].

Targeted drug therapy is crucial for MM, as studies show that combination therapies significantly enhance treatment efficacy and prolong survival [10, 11]. Bortezomib, a novel anti-MM drug, significantly downregulates tumor necrosis factor-κB activity. Combined with dexamethasone, it can induce apoptosis in drug-resistant cells and enhance drug sensitivity at tumor sites [12, 13]. Lenalidomide effectively induces tumor cell apoptosis, inhibits angiogenesis, regulates

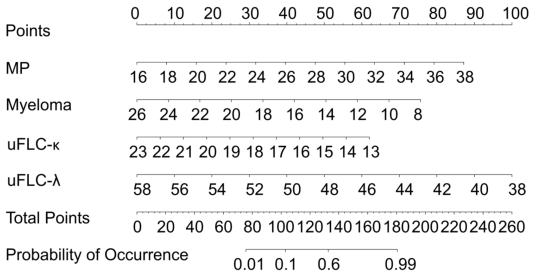

Figure 4. Nomogram model. MP: monoclonal protein; FLC: Free Light Chain.

immunity, and has minimal neurotoxicity and high safety [14]. In the course of this investigation, it was ascertained that the lenalidomide group manifested superior clinical efficacy in juxtaposition. It may be likely because combination therapy rapidly reduces tumor burden and achieves deep remission early. As MM drugs evolve, plasma cells proliferate malignantly, producing abnormal immune M globulins, while lymphocytes secrete β_2-microglobulin [15]. The development of MM is often associated with immune imbalances in patients [16]. Dexamethasone, with anti-inflammatory and anti-allergic properties, inhibits immune responses, and mildly affects sodium retention [17, 18]. Lenalidomide regulates immunity and kills tumor cells [19]. Bortezomib inhibits the 20s proteasome B5 subunit, curbing plasma cell proliferation. Combining bortezomib and lenalidomide with dexamethasone can enhance immune function. In this research, a marked reduction in the levels of bone marrow plasma cells, M protein, and free light chains was noted in patients with lenalidomide. These findings suggest that the therapeutic regimen combining bortezomib, lenalidomide, and dexamethasone is effective in boosting immune function among MM patients. The proliferation and viability of MM cells are linked to the expression levels of diverse cytokines. LDH levels reflect tumor burden and contribute to disease progression [20]. Bortezomib combined with dexamethasone and lenalidomide chemotherapy can inhibit T and B cell proliferation and differentiation, selectively target abnormal plasma cell clonal expansion, boost cytokine production, and suppress pro-inflammatory factors, thereby reducing inflammation [21, 22]. This mechanism effectively curbs the proliferation and diffusion of MM cells. Lenalidomide, an immunomodulator, enhances the immune response in the tumor microenvironment by boosting T cell and natural killer cell activity, promoting tumor cell recognition and clearance, and inhibiting tumor growth [23, 24]. Combined with bortezomib, which directly targets and kills tumor cells, it creates a synergistic effect that enhances MM treatment efficacy [25]. Moreover, bortezomib and lenalidomide improve biochemical abnormalities like anemia and hypercalcemia, which often accompany MM and can worsen disease progression and quality of life [26, 27]. As important indicators of plasma cell malignancy, FLC-κ and FLC-λ hold significant diagnostic and prognostic value in MM [28]. The decline in these markers post-treatment indicates that lenalidomide may offer clinical benefits for patients with this hematologic malignancy. Post-treatment analysis revealed significantly lower Scr and BUN levels in the lenalidomide group compared to controls, indicating its potential to enhance renal function. Scr and BUN serve as reliable markers of glomerular filtration rate (GFR). Impaired renal parenchyma leads to diminished GFR, elevating Scr and BUN levels due to compromised excretory function. As a widely adopted clinical assessment tool, VAS scores effectively evaluate treatment outcomes in MM. Following intervention, both treatment arms exhibited marked pain reduction, with lenalidomide-treated patients achieving significantly lower scores than the control group. This combination therapy leverages the synergistic effects of different drugs, enhancing treatment tolerance and compliance in MM patients [29]. Within the scope of this research, variations between groups were also noted in diarrhea, thrombocytopenia, neutropenia, anemia, limb oedema, and fever due to bortezomib [30, 31].

In medical studies, logistic regression serves as a fundamental statistical approach for assessing associations between biomarkers and disease outcomes. To visualize these relationships, researchers often employ nomograms. Model performance is typically evaluated using ROC curves, quantifying predictive accuracy through the AUC. A higher AUC indicates better discrimination between true positives and false positives [32]. In this study, the model achieved an AUC of 0.942, demonstrating robust predictive capability. Calibration analysis further confirmed strong alignment be-

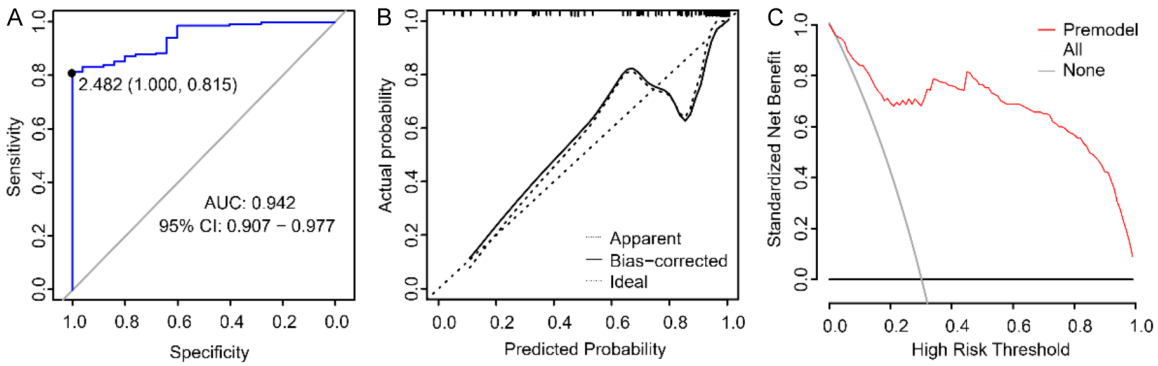

Figure 5. Verification of the model. A. The ROC curve of the nomogram model; B. The calibration curve of the nomogram model; C. The decision curve of the nomogram model.

tween predicted and observed outcomes, suggesting high clinical reliability. Therefore, lenalidomide combined with bortezomib and dexamethasone had a certain effect on immune function.

Conclusion

In summary, the combination of lenalidomide, bortezomib, and dexamethasone was associated with favorable clinical outcomes in MM patients, making it a promising option for clinical application. Nonetheless, this study is constrained due to its limited sample size and single-center retrospective approach. This article does not study the indicators directly related to immunity, which will be further improved in future research. Future research will focus on conducting multi-center, prospective trials to increase the sample size and examine the therapeutic benefits and potential risks of the regimen that includes lenalidomide, bortezomib, and dexamethasone for treating multiple myeloma.

Disclosure of conflict of interest

None.

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