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High levels of serum IL-10 indicate disease progression, extramedullary involvement, and poor prognosis in multiple myeloma

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Multiple myeloma (MM) is a common malignant hematological tumor in adults, which is characterized by clonal malignant proliferation of plasma cells in the bone marrow and secretion of a large number of abnormal monoclonal immunoglobulins (M protein), leading to bone destruction, hypercalcemia, anemia, and renal insufficiency (Alexandrakis et al., 2015; Yang et al., 2018). Since a large number of new drugs, represented by proteasome inhibitors and immunomodulators, have been successfully used to treat MM, treatment efficacy and survival of patients have been significantly improved. However, due to the high heterogeneity of this disease, patients have responded differently to treatments with these new drugs (Palumbo and Anderson, 2011; Wang et al., 2016; Huang et al., 2020). Growth and survival of MM cells depend on the bone marrow microenvironment, especially numerous inflammatory cytokines secreted by myeloma cells and bone marrow stromal cells, such as vascular endothelial growth factor (VEGF), interleukin (IL)-6, transforming growth factor-β (TGF-β), and IL-10. These cytokines can promote the growth of myeloma cells, induce angiogenesis, and inhibit antitumor immunity, and are often linked to patient prognosis (Kumar et al., 2017). In this era of new drugs, the prognostic values of the serum levels of these cytokines in MM need further evaluation.

Therefore, in this study we retrospectively analyzed the prognostic values of peripheral blood inflammatory factor levels for newly diagnosed MM (NDMM) patients treated with bortezomib as first-line therapy.

A total of 157 NDMM patients chosen according to 2014 International Myeloma Working Group (IMWG) diagnostic criteria (Rajkumar et al., 2014) were enrolled. They were first seen and treated in the First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou) between November 2014 and September 2018. Patients received a bortezomib-based regimen as the first-line induction treatment (He et al., 2020). Young and physically fit patients with partial remission or better efficacy voluntarily chose to receive autologous stem cell transplantation (ASCT). Then patients were treated with dexamethasone combined with bortezomib or lenalidomide for 2–3 years or until the disease progressed. The clinical characteristics of the NDMM patients at baseline are shown in Table 1.

All of the NDMM patients were tested for peripheral blood cytokine levels, including IL-2, IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-17A, before the first dose of anti-myeloma treatment. We quantified serum concentrations of the seven aforementioned cytokines using the BD™ Cytometric Bead Array (CBA) Human Th1/Th2/

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Table 1 Baseline characteristics of NDMM patients

Baseline characteristics	Data
Total	157
Age (years)	64 (44–80)
Male	89 (56.7%)
D-S	
1+2+3A	131 (83.4%)
3B	26 (16.6%)
ISS	
1+2	99 (63.1%)
3	58 (36.9%)
R-ISS (*n*=147)	
1+2	108 (73.5%)
3	39 (26.5%)
CRP (mg/L)	2.0 (0–204.2)
LDH (U/L)	180 (79–5785)
Cr (μmol/L)	88 (39–1033)
IL-2 (pg/mL)	0.10 (0.10–11.74)
IL-4 (pg/mL)	0.10 (0.10–6.01)
IL-6 (pg/mL)	4.32 (0.10–1657.79)
IL-10 (pg/mL)	0.48 (0.10–49.26)
TNF-α (pg/mL)	0.10 (0.10–108.90)
IFN-γ (pg/mL)	0.10 (0.10–17.61)
IL-17A (pg/mL)	0.10 (0.10–21.02)
Genetic abnormalities (*n*=142)	
Standard risk	62 (43.7%)
High risk	80 (56.3%)
BMPC percentage (%)	27.0 (0–97.0)
Therapy received	
PD	32 (20.4%)
PAD	22 (14.0%)
PCD	91 (58.0%)
PTD	5 (3.2%)
ASCT	20 (12.7%)

Data are presented as median (range) or number (percentage). NDMM: newly diagnosed multiple myeloma; D-S: Durie-Salmon staging; ISS: international staging system; R-ISS: revised ISS; CRP: C-reactive protein; LDH: lactate dehydrogenase; Cr: creatinine; IL-2: interleukin-2; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-γ; BMPC: bone marrow plasma cell; PD: bortezomib, dexamethasone; PAD: bortezomib, dexamethasone, adriamycin; PCD: bortezomib, dexamethasone, cyclophosphamide; PTD: bortezomib, dexamethasone thalidomide; ASCT: autologous stem cell transplantation.

Th17 Cytokine Kit (BD Biosciences, San Jose, CA, USA).

The optimal cutoff value of cytokines was based on the receiver operating characteristic (ROC) curve. According to the ROC curve, the best cutoff value for serum IL-10 was 1.42 pg/mL, with an area under the curve (AUC) value of 0.726, and the sensitivity and specificity were 65.3% and 79.6%, respectively (Fig. 1). Overall, 103 patients (65.6%) were classified into the low IL-10 group, and 54 (34.4%) patients were classified into the high IL-10 group. The optimal cutoff values of all indicators are presented in Tables 2 and 3.

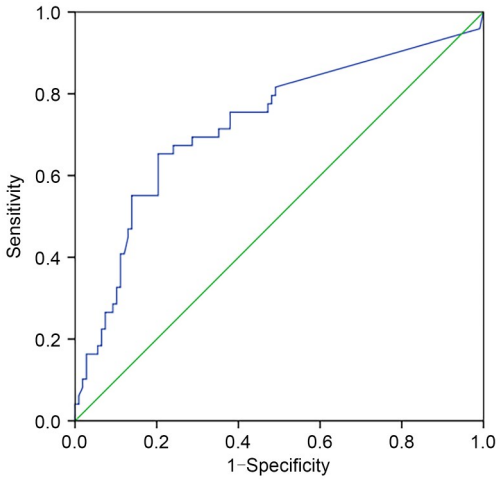

Fig. 1 Optimal cutoff value of serum interleukin-10 (IL-10).

All NDMM patients were followed up until June 30, 2020. The median duration of follow-up was 30.5 months (95% confidence interval (CI): 1.1–67.1 months), the median progression-free survival (PFS) time was 29.2 months (95% CI: 21.8–36.5 months), and the median overall survival (OS) was not reached. We used Cox proportional hazards model to perform univariate and multivariate analyses (Tables 2 and 3). Univariate analysis showed that higher serum IL-10 level was tied to worse PFS and OS in NDMM patients, and serum IL-10 level was also an independent factor for poor OS in NDMM patients. This result was in line with the study by Shekarriz et al. (2018). However, other serum cytokine levels did not affect PFS or OS in NDMM patients treated with bortezomib. IL-10 is a major inflammatory inhibitor in the tumor microenvironment (TME), mainly secreted by monocytes/macrophages, T lymphocytes, B lymphocytes, natural killer (NK) cells, and mast cells (Musolino et al., 2017), and participates in the pathophysiological development of a variety of hematological malignancies, including chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), and MM. It is negatively correlated with prognosis for the disease (Fayad et al., 2001; Načinović-Duletić et al., 2008; Gupta et al., 2012; Shekarriz et al., 2018).

Then we analyzed the survival of patients with different serum IL-10 levels. Using the Kaplan-Meier

Table 2 Univariable and multivariable analyses for PFS of NDMM patients

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (>55 years)	0.96 (0.58–1.60)	0.877		
D-S (3B vs. 1+2+3A)	1.74 (1.02–2.94)	0.044	2.01 (1.09–3.68)	0.024
ISS (3 vs. 1+2)	1.98 (1.13–3.47)	0.542		
R-ISS (3 vs. 1+2)	1.54 (0.95–2.49)	0.077		
CRP (≥1.18 mg/L)	1.11 (0.71–1.73)	0.663		
LDH (≥250 U/L)	2.49 (1.47–4.20)	0.001		
Cr (≥177 μmol/L)	1.61 (0.93–2.78)	0.090		
IL-2 (≥0.22 pg/mL)	1.28 (0.80–2.04)	0.310		
IL-4 (≥0.75 pg/mL)	0.89 (0.38–2.07)	0.778		
IL-6 (≥0.49 pg/mL)	0.90 (0.50–1.59)	0.706		
IL-10 (≥1.42 pg/mL)	1.58 (1.02–2.46)	0.040		
TNF-α (≥0.17 pg/mL)	0.92 (0.59–1.44)	0.726		
IFN-γ (≥0.52 pg/mL)	1.03 (0.60–1.80)	0.908		
IL-17A (≥2.51 pg/mL)	1.17 (0.66–2.09)	0.592		
BMPC percentage (≥30%)	1.97 (1.27–3.07)	0.002	1.90 (1.20–3.01)	0.007
Genetic abnormalities (high risk)	2.16 (1.34–3.50)	0.001		
Extramedullary lesions (Yes)	5.32 (1.92–14.77)	<0.001	5.69 (1.36–23.75)	0.017
Treatment response (<PR)	6.42 (3.04–13.52)	<0.001	4.95 (1.59–15.43)	0.006

PFS: progression-free survival; NDMM: newly diagnosed multiple myeloma; HR: hazard ratio; CI: confidence interval; D-S: Durie-Salmon staging; ISS: international staging system; R-ISS: revised ISS; CRP: C-reactive protein; LDH: lactate dehydrogenase; Cr: creatinine; IL-2: interleukin-2; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-γ; BMPC: bone marrow plasma cell; PR: partial remission.

Table 3 Univariable and multivariable analyses for OS of NDMM patients

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (>55 years)	2.65 (1.05–6.71)	0.032		
D-S (3B vs. 1+2+3A)	3.56 (1.94–6.42)	<0.001		
ISS (3 vs. 1+2)	2.51 (1.42–4.43)	0.002		
R-ISS (3 vs. 1+2)	3.27 (1.79–5.98)	<0.001	2.87 (1.47–5.62)	0.002
CRP (≥1.18 mg/L)	1.60 (0.85–3.03)	0.145		
LDH (≥250 U/L)	4.70 (2.60–8.51)	<0.001		
Cr (≥177 μmol/L)	3.70 (2.03–6.75)	<0.001		
IL-2 (≥0.22 pg/mL)	0.76 (0.34–1.70)	0.505		
IL-4 (≥0.75 pg/mL)	1.66 (0.67–4.12)	0.278		
IL-6 (≥0.49 pg/mL)	0.64 (0.32–1.29)	0.642		
IL-10 (≥1.42 pg/mL)	4.68 (2.59–8.44)	<0.001	4.32 (2.23–8.39)	<0.001
TNF-α (≥0.17 pg/mL)	1.10 (0.62–1.97)	0.741		
IFN-γ (≥0.52 pg/mL)	1.74 (0.93–3.24)	0.078		
IL-17A (≥2.51 pg/mL)	1.46 (0.73–2.94)	0.286		
BMPC percentage (≥30%)	2.26 (1.25–4.10)	0.007	2.17 (1.14–4.16)	0.019
Genetic abnormalities (high risk)	2.72 (1.36–5.47)	0.003		
Extramedullary lesions (Yes)	7.45 (2.54–21.79)	<0.001		
Treatment response (<PR)	8.18 (3.75–17.83)	<0.001	10.82 (3.71–31.52)	<0.001

OS: overall survival; NDMM: newly diagnosed multiple myeloma; HR: hazard ratio; CI: confidence interval; D-S: Durie-Salmon staging; ISS: international staging system; R-ISS: revised ISS; CRP: C-reactive protein; LDH: lactate dehydrogenase; Cr: creatinine; IL-2: interleukin-2; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-γ; BMPC: bone marrow plasma cell; PR: partial remission.

method to generate survival curves, we compared the difference between the curves using the log-rank test. Patients in the high IL-10 group had worse PFS and OS than those in the low IL-10 group (P=0.040 and P<0.001, respectively). The median PFS was 17.7 months (95% CI: 13.7–21.7 months) and 33.2 months (95% CI: 26.6–39.8 months) for the high and low IL-10 groups, respectively (Fig. 2a), and the median OS was 28.5 months (95% CI: 20.9–36.0 months) and not reached, respectively (Fig. 2b). However, the mechanism of IL-10 leading to poor survival in MM patients has not been fully elucidated. In diffuse large B cell lymphoma (DLBCL), it has been reported that IL-10 signaling can activate the Janus kinase (JAK) signaling pathway in lymphoma cells and promote expression of oncogenes, such as *c-myc*. The same study suggested that serum IL-10 might be a biomarker to identify patients that are more likely to respond to JAK inhibitors (Gupta et al., 2012). In addition to acting directly on tumor cells and TME, IL-10, as an important immunosuppressive cytokine, has the additional effect of blocking anti-tumor immunity (Minnie et al., 2018).

Subsequently, we analyzed the relationship between serum IL-10 and clinical characteristics and therapy efficacy. The results indicated that high serum IL-10 was associated with high risk in there different staging systems: Durie-Salmon staging (D-S), international staging system (ISS), and revised ISS (R-ISS). In addition, patients with high serum IL-10 were more likely to have anemia or thrombocytopenia, elevated serum lactate dehydrogenase (LDH), C-reactive protein (CRP), or creatinine (Cr) level, and high-risk cytogenetic abnormalities (17p−, 1q+, and immunoglobulin heavy-chain (IgH) translocation) (Table 4). The treatment efficacy in 157 patients was evaluated after treatment. The overall response rates (ORRs) in the low and high IL-10 groups were 96.1% and 90.7% (P=0.169), the complete remission (CR) rates were 45.6% and 40.7% (P=0.558), and ⩾very good partial remission rates (VGPRs) were 65.0% and 57.4% (P=0.348), respectively. In the study by Wang et al. (2016), 55.3% (104/188) of patients received the traditional chemotherapy regimen, and it was confirmed that serum IL-10 levels were negatively correlated with treatment efficacy. However, our study did not find a significant correlation between elevated IL-10 serum levels and treatment efficacy, possibly because all patients in our study were treated with a bortezomib-based regimen that overcame the adverse effects of serum IL-10 to a certain extent.

The serum IL-10 concentration in MM patients has been found to be significantly higher than that in healthy volunteers (Shekarriz et al., 2018). Therefore, we recruited 15 age-matched healthy volunteers and 96 refractory/relapsed MM (RRMM) patients treated in our hospital during the same period, so that we could test and compare the differences in serum IL-10 levels among healthy volunteers, NDMM, and RRMM patients. The 15 healthy volunteers included nine males and six females with a median age of 61 years (range, 48–71 years), and there was no statistical

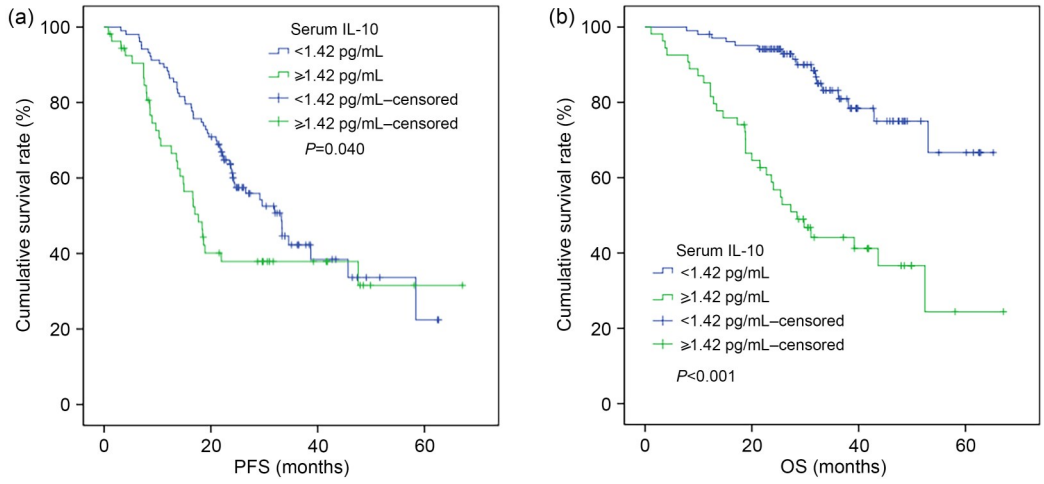

Fig. 2 Relationship between serum IL-10 level and survival of NDMM patients. (a) PFS of patients based on serum IL-10 level; (b) OS of patients based on serum IL-10 level. IL-10: interleukin-10; NDMM: newly diagnosed multiple myeloma; OS: overall survival; PFS: progression-free survival.

Table 4 Correlation of serum IL-10 with patient baseline clinical characteristics

Characteristics	IL-10		*P* value
	<1.42 pg/mL (*n*=103)	≥1.42 pg/mL (*n*=54)	
Age (years)			
≤55	37 (35.9%)	25 (46.3%)	0.207
>55	66 (64.1%)	29 (53.7%)	
Sex			
Male	59 (57.3%)	30 (55.6%)	0.836
Female	44 (42.7%)	24 (44.4%)	
D-S			
1+2+3A	96 (93.2%)	35 (64.8%)	**<0.001**
3B	7 (6.8%)	19 (35.2%)	
ISS			
1	44 (42.7%)	9 (16.7%)	**0.003**
2	28 (27.2%)	18 (33.3%)	
3	31 (30.1%)	27 (50.0%)	
R-ISS			
1	16 (15.5%)	2 (3.7%)	**0.008**
2	63 (61.2%)	27 (50.0%)	
3	18 (17.5%)	21 (38.9%)	
Hb (g/L)			
<80	21 (20.4%)	22 (40.7%)	**0.007**
≥80	82 (79.6%)	32 (59.3%)	
Plt ($\times10^9$ L^{-1})			
<150	32 (31.1%)	26 (48.1%)	**0.035**
≥150	71 (68.9%)	28 (51.9%)	
LDH (U/L)			
<250	95 (92.2%)	35 (64.8%)	**<0.001**
≥250	8 (7.8%)	19 (35.2%)	
CRP (mg/L)			
<1.18	44 (42.7%)	13 (24.7%)	**0.021**
≥1.18	59 (57.3%)	41 (75.9%)	
Cr (μmol/L)			
<177	97 (94.2%)	34 (63.0%)	**<0.001**
≥177	6 (5.8%)	20 (37.0%)	
BMPC percentage (%)			
<30	60 (58.3%)	31 (57.4%)	0.919
≥30	43 (41.7%)	23 (42.6%)	
Genetic abnormalities			
Standard risk	46 (50.5%)	16 (31.4%)	**0.027**
High risk	45 (49.5%)	35 (68.6%)	
Extramedullary lesions			
No	101 (98.1%)	51 (94.4%)	0.340
Yes	2 (1.9%)	3 (5.6%)	
Treatment response			
≥PR	99 (96.1%)	49 (90.7%)	0.169
<PR	4 (3.9%)	5 (9.3%)	

P value of <0.05 is in bold. IL-10: interleukin-10; D-S: Durie-Salmon staging; ISS: international staging system; R-ISS: revised ISS; Hb: hemoglobin; Plt: platelets; CRP: C-reactive protein; LDH: lactate dehydrogenase; Cr: cre`atinine; BMPC: bone marrow plasma cell; PR: partial remission.

difference in the gender or age between NDMM patients and healthy volunteers (*P*=0.825 and *P*=0.509, respectively). The median prior regimen of 96 RRMM patients was 3 (range, 1–5), including 60 males (62.5%) and 36 females (37.5%), and the median age was 60 years (range, 41–80 years). There were no differences in baseline clinical characteristics between RRMM and NDMM patients. Our findings showed that the median concentration of serum IL-10 in healthy volunteers was 0.10 pg/mL (range, 0.10–0.71 pg/mL), significantly lower than that in NDMM patients (0.48 pg/mL (range, 0.10–49.26 pg/mL); *P*=0.002), while the median concentration of serum IL-10 in RRMM patients was 2.55 pg/mL (range, 0.10–1916.74 pg/mL), significantly higher than that in NDMM patients (*P*<0.001; Fig. 3). Further prospective studies should be conducted in the initial and relapsed cases of the same group of MM patients to further confirm the correlation between serum IL-10 level and disease status.

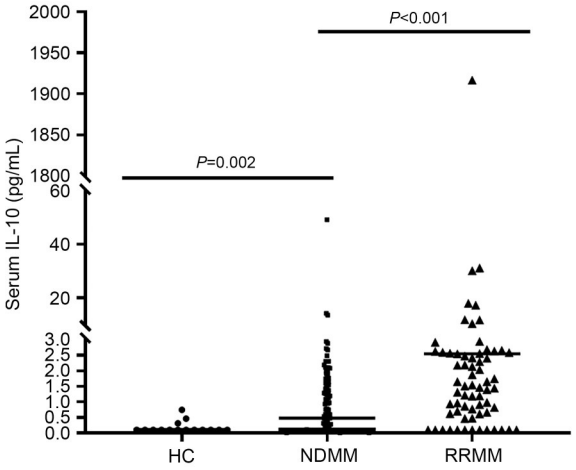

Fig. 3 Comparison of serum interleukin-10 (IL-10) concentrations between healthy control (HC), newly diagnosed multiple myeloma (NDMM) patients, and refractory/relapsed multiple myeloma (RRMM) patients.

Most MM cells are confined to the bone marrow, and in some cases, malignant plasma cells can involve paraosseous tissue, known as extramedullary-bone related (EM-B), and even enter the blood circulation and colonize distant tissue to form extramedullary-extraosseous (EM-E) lesions. However, it is generally assumed that EM-B does not significantly affect patient survival, while patients with EM-E have very poor survival rates (He et al., 2021). In a single-cell sequencing study involving a small sample, it was

found that tumor cells in extramedullary MM lesions had higher expression of IL-10 and its receptor than those in intramedullary MM cells (Ryu et al., 2020); however, no studies have yet suggested a correlation between serum IL-10 level and EME. In this study, there were a total of 19 patients who had EME involvement of the 253 patients with NDMM and RRMM, 5 (3.2%) NDMM and 14 (14.6%) RRMM patients. The serum IL-10 levels of the 19 EME patients were significantly higher than those of patients without EME involvement, 5.90 pg/mL (range, 0.10–1916.74 pg/mL) vs. 1.07 pg/mL (range, 0.10–66.79 pg/mL) (P<0.001).

In summary, our study confirmed that serum IL-10 levels are associated with disease progression and high-risk clinical characteristics, and significantly affect PFS and OS in NDMM patients. Additionally, the cox proportional hazards model demonstrated that serum IL-10 is an independent prognostic factor for OS among NDMM patients treated with bortezomib-based regimens. Therefore, as a simple, economical prognostic indicator, serum IL-10 could be applied in clinical work because it has significant prognostic value for MM patients. Nonetheless, this conclusion needs to be validated by prospective research using a larger number of cases.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

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Author contributions

Xiaoyan YUE wrote and translated part of the manuscript, reviewed literature, managed the patients, and collected clinical data. Linlin HUANG, Yang YANG, Yi ZHAO, Donghua HE, Xiaoyan HAN, Gaofeng ZHENG, Yi LI, Enfang ZHANG, Zhen CAI, and Xin HUANG reviewed and wrote a part of the manuscript and provided suggestions. Jingsong HE wrote a part of the manuscript, reviewed the literature, managed the patients, collected clinical data, and provided suggestions. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Xiaoyan YUE, Linlin HUANG, Yang YANG, Yi ZHAO, Donghua HE, Xiaoyan HAN, Gaofeng ZHENG,Yi LI, Enfan ZHANG, Zhen CAI, Xin HUANG, and Jingsong HE declare that they have no conflict of interest.

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University (No. IIT20210091A). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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Supplementary information

Materials and methods