

Clinical impact of echocardiography-defined pulmonary hypertension on the clinical outcome in patients with multiple myeloma

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Abstract

Pulmonary hypertension (PH) is a complication of multiple myeloma (MM); however, the clinical outcomes and prognosis are relatively not well known. We aimed to investigate the risk factors of transthoracic echocardiography-defined PH and its impact on the clinical outcome in patients with MM.

A retrospective study was performed using data from the Chonnam National University Hwasun Hospital database for patients who underwent transthoracic echocardiography (TTE) within 1 month of the MM diagnosis between January 2007 and December 2017. PH was defined as an estimated right ventricular systolic pressure (RVSP) > 40 mmHg. A total of 390 patients were included. TTE-defined PH was observed in 107 patients (27%). During the follow-up period (median, 688 days), all-cause death was noted for 134 patients (34.4%). In the Kaplan-Meier survival analysis, the cumulative overall survival and cardiovascular death-free survival rates were significantly lower in the PH group than in the non-PH group ($P < .001$). In the propensity score-matched population, RVSP > 40 mmHg on TTE and history of congestive heart failure (CHF) were identified as the significant independent predictors of all-cause and cardiovascular death.

This study reports that the prevalence of TTE-defined PH is higher in patients with MM than in the general population. Moreover, TTE-defined PH and a history of CHF are the independent prognostic factors for all-cause and cardiovascular death in patients with MM. These results highlight the risk of associated cardiovascular disease in patients with MM and emphasize the importance of management strategies that prevent the deterioration of cardiac function.

Abbreviations: ADHF = decompensated heart failure, AL = light chain, ASE = American Society of Echocardiography, ASR = age-standardized incidence rate, CHF = congestive heart failure, DM = diabetes mellitus, DT = deceleration time of mitral inflow, eGFR = estimated glomerular filtration rate, GLS = global longitudinal strain, Ig = immunoglobulin, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, MI = myocardial infarction, MM = multiple myeloma, PAP = pulmonary arterial pressure, PH = pulmonary hypertension, PSM = propensity score-matched, RAP = right atrial pressure, RVSP = right ventricular systolic pressure, TRV = tricuspid regurgitation velocity, TTE = transthoracic echocardiography, WHO = World Health Organization.

Keywords: multiple myeloma, pulmonary hypertension, echocardiography, mortality

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1. Introduction

Multiple myeloma (MM) is caused by the malignant proliferation of plasma cells derived from monoclonal antibodies, and it can lead to multiple organ dysfunction, including that of the heart. The presence of several features, such as hypercalcemia, renal failure, anemia, and hemolytic bone lesions, distinguishes MM from other types of plasma cell proliferation.^[1] According to the 2012 International Agency for Research on Cancer Data, MM has a worldwide age-standardized incidence rate (ASR) of 1.5/100,000, and the Asian countries have lower ASRs of MM than the Western countries.^[2] However, there has been a two-fold increase in the incidence of MM in Asia over the last 10 years, which is striking considering that the 2012 Korean data on national cancer statistics indicated that the ASR of MM was 10 times higher than that recorded 20 years ago.^[3] As the management of MM improves, the life expectancy at diagnosis has improved significantly.^[4] However, only a small number of patients survive for more than 10 years.^[5]

Pulmonary hypertension (PH), characterized by elevated pulmonary artery pressure and pulmonary vascular resistance, is a pathophysiological disorder that is a composite of the major cardiovascular and respiratory diseases. The World Health Organization (WHO) has classified PH into 5 groups according to the similarities in the pathophysiologic mechanisms and clinical presentation.^[6] Although PH in MM has been rarely reported, the possible etiologies of PH in MM include left heart systolic disease, diastolic dysfunction (group 2), chronic thromboembolic PH resulting from thrombophilia (group 4), and adverse effects of various chemotherapy agents, in particular thalidomide/lenalidomide (group 1). PH has been reported as a complication of MM and other related monoclonal cell disorders in several cases.^[7–10] The use of immunomodulating therapy is also an independent risk factor for PH.^[11,12] However, only a few studies have reported on PH with respect to the incidence and prognosis of MM. The current study aimed to investigate the risk factors of transthoracic echocardiography (TTE)-defined PH and its impact on the clinical outcomes in patients with MM.

2. Material and methods

2.1. Study design and population

We enrolled 529 patients with MM who underwent TTE in Chonnam National University Hwasun Hospital between January 2007 and December 2017. Patients with pathologically proven involvement with amyloid light chain (AL) amyloidosis were excluded from the analysis. After excluding 139 patients who underwent TTE more than 1 month after the diagnosis of MM to minimize the cardiac effects of chemotherapy and other factors, a total of 390 patients were included and divided into 2 groups, namely, patients without PH and patients with PH, based on the TTE results. The study protocol was approved by the Chonnam National University Hospital Institutional Review Board (IRB number: 2015-05-092).

2.2. Study definitions

MM was diagnosed by bone marrow biopsy and confirmed by a hematologist. Based on the available literature, PH was defined by an estimated right ventricular systolic pressure (RVSP) > 40 mmHg on TTE.^[13] We collected information on the baseline demographic characteristics, treatment history, laboratory

findings, TTE characteristics, and clinical outcomes for all patients. We stratified the enrolled population according to several criteria, including the Revised International Staging System (based on the serum $\beta 2$ microglobulin and albumin levels).

Hypertension was defined as a history of hypertension diagnosed and treated with medication, systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg on at least 2 occasions, or current antihypertensive pharmacological therapy. Diabetes mellitus (DM) was defined as a history of DM, regardless of the duration of disease, need for antidiabetic agents, fasting blood glucose > 126 mg/dL, or HbA1c \geq 6.5%. Congestive heart failure (CHF) was defined according to the New York Heart Association Classification III and IV symptoms.

To minimize interference of various treatments, we reviewed the treatment history of autologous peripheral blood stem cell transplantation and chemotherapy regimens. The primary outcome was all-cause death. The definition of cardiovascular death included acute decompensated heart failure (ADHF), myocardial infarction (MI), and sudden cardiac arrest. ADHF was diagnosed using the criteria of the current guidelines.^[14] Briefly, a diagnosis of ADHF was based on clinical symptoms, such as dyspnea and fatigue, and signs, such as peripheral edema and pulmonary congestion using the Framingham criteria. If ADHF was caused by a condition other than coronary ischemia, the patient was considered not to have ADHF. The term “hopeless discharge” was used in cases where the patients with do-not-resuscitate consent were transferred to a hospice ward or ointment hospitals.

2.3. Echocardiographic examination

According to the current American Society of Echocardiography (ASE) guidelines, comprehensive echocardiography was used for analysis. Echocardiography images were obtained using two different commercially available echocardiography equipment systems (Vivid 7 and Vivid E9, GE Vingmed Ultrasound, Horten, Norway).

Chamber quantifications were performed according to the current ASE guidelines and included measurements of left ventricular (LV) end-diastolic and end-systolic dimensions (LVEDD and LVESD, respectively), left atrial diameter (LAD), and LV ejection fraction.^[15] The early (E wave) and late (A wave) diastolic velocity of the mitral inflow were measured using the apical 4-chamber view during pulsed-wave Doppler, with the sample volume located at the tip of the mitral leaflets. The deceleration time of the E wave was measured as the time between the peak early diastolic velocity and the point at which the steepest deceleration slope was extrapolated to the zero line. The early diastolic (E' wave) and late diastolic (A' wave) of the septal mitral annulus were obtained using tissue Doppler imaging in the apical 4-chamber view. Diastolic dysfunction categorization was based on the E/A ratio. Grade 1 diastolic dysfunction was determined if the E/A ratio was < 0.8, and an E/A ratio of 0.8–1.5 was classified as grade 2 diastolic dysfunction, and E/A > 1.5 as grade 3.^[16]

We measured the myocardial strain parameter of global longitudinal strain (GLS) using the standard methodology for speckle tracking.^[17] After manual tracing of the LV endocardial border, the dedicated software automatically tracked the myocardium throughout the cardiac cycle in the apical 4-chamber, 2-chamber, and long-axis views. The GLS was obtained by averaging the peak values of segmental strain in the apical views.^[18]

The peak tricuspid regurgitation velocity was measured using Doppler echocardiography to estimate the RVSP with the modified Bernoulli formula. Since the diameter of the inferior caval vein and its respiratory variation are poorly related to the right atrial pressure (RAP), we did not add the RAP to the RVSP to estimate the systolic pulmonary arterial pressure.^[19]

2.4. Statistical analysis

All continuous variables are presented as means±standard deviation, and discrete variables are expressed as counts and percentages. The differences between the groups were evaluated using the two-sample *t* test, χ^2 tests, or Fisher exact test, as appropriate. We prepared Kaplan-Meier curves for all-cause and cardiovascular death according to the PH and non-PH groups. Since the differences in the baseline characteristics could significantly affect the outcomes, sensitivity analyses were performed to adjust for confounding factors.

First, the following covariates were used in the multivariable Cox regression model: age ≥ 65 years, hypertension, DM, previous history of CHF, coronary artery disease, estimated glomerular filtration rate (eGFR) > 60 mL/min, immunoglobulin (Ig) A > 500 mg/dL, RVSP > 40 mmHg, LAD > 40 mm, $E' < 0.07$ m/s, $E/E' > 14$, and ejection fraction $< 50\%$.

Second, Cox proportional hazard regression analysis was performed for the propensity score-matched cohort. The propensity score was estimated for the choice of PH using a

multivariable logistic regression model that contained 22 covariates. The C-statistic of the logistic-regression model for propensity score matching was 0.702. The percent standardized mean differences after propensity score matching were within 10% across all matched covariates, indicating successful balance between the groups being compared.

All analyses were two-tailed, and a *P* value $< .05$ was considered to indicate significance. All statistical analyses were performed using the R Core Team (2015) (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

3. Results

3.1. Baseline clinical characteristics, history of treatment, and laboratory findings

TTE-defined PH was observed in 107 patients (27%). The patients in the PH group were older (68.8 ± 7.8 vs 65.9 ± 9.6 years, $P = .002$) than those in the non-PH group (Table 1). There was no significant difference in the treatment, with the exception of cyclophosphamide administration, between the PH and non-PH groups. The laboratory findings indicated that the PH group had lower white blood cell counts (9.4 ± 6.3 vs 12.7 ± 23.8 10³/L, $P = .04$) and eGFR (43.7 ± 27.6 vs 51.0 ± 31.1 mL/min/1.73 m², $P = .039$) and a higher level of serum IgA ($1,489.6 \pm 2,472.0$ vs $741.6 \pm 1,585.6$ mg/dL, $P = .034$) compared to the non-PH group (Table 2).

Table 1

Baseline clinical characteristics and treatment history.

Variable	Crude population			Propensity score-matched population			
	Non-PH (N=283)	PH (N=107)	<i>P</i> value	Non-PH (N=96)	PH (N=96)	<i>P</i> value	SMD (%)
Demographics							
Age at diagnosis (y)	65.9±9.6	68.8±7.8	.002	68.0±8.7	68.4±7.6	.677	6.06%
Male	160 (56.5)	55 (51.4)	.426	47 (45.2)	53 (51.0)	.488	9.49%
R-ISS stage			.053			.774	9.69%
I	11 (3.9)	1 (0.9)		1 (1.0)	1 (1.0)		
II	187 (66.1)	62 (57.9)		66 (63.5)	61 (58.7)		
III	85 (30.0)	44 (41.1)		37 (35.6)	42 (40.4)		
Cardiovascular risk factors							
Hypertension	105 (37.1)	49 (45.8)	.147	44 (42.3)	47 (45.2)	.780	5.76%
Diabetes mellitus	65 (23.0)	22 (20.6)	.709	21 (20.2)	22 (21.2)	1.000	2.37%
History of CHF	24 (8.5)	15 (14.0)	.151	10 (9.6)	9 (8.7)	1.000	3.29%
History of CAD	13 (4.6)	9 (8.4)	.225	10 (9.6)	10 (9.6)	1.000	0.00%
History of CVA	9 (3.2)	1 (0.9)	.372	0 (0.0)	1 (1.0)	1.000	9.95%
Pulmonary VTE	13 (4.6)	2 (1.9)	.340	4 (3.8)	2 (1.9)	.679	9.13%
COPD	12 (4.2)	9 (8.4)	.169	8 (7.7)	8 (7.7)	1.000	0.00%
History of treatment							
Autologous PBSCT	75 (26.5)	20 (18.7)	.141	21 (20.2)	20 (19.2)	1.000	2.45%
Bortezomib	222 (78.4)	87 (81.3)	.630	88 (84.6)	84 (80.8)	.582	9.82%
Cyclophosphamide	239 (84.5)	79 (73.8)	.023	80 (76.9)	79 (76.0)	1.000	2.18%
Thalidomide	138 (48.8)	41 (38.3)	.083	39 (37.5)	41 (39.4)	.887	3.94%
Lenalidomide	116 (41.0)	36 (33.6)	.226	33 (31.7)	36 (34.6)	.768	6.08%
Etoposide	53 (18.7)	16 (15.0)	.470	15 (14.4)	16 (15.4)	1.000	2.68%
Doxorubicin	16 (5.7)	6 (5.6)	1.000	5 (4.8)	6 (5.8)	1.000	4.16%
Cisplatin	9 (3.2)	4 (3.7)	1.000	3 (2.9)	4 (3.8)	1.000	5.05%
Pomalidomide	31 (11.0)	7 (6.5)	.263	4 (3.8)	7 (6.7)	.536	8.61%
Daratumumab	9 (3.2)	4 (3.7)	1.000	3 (2.9)	4 (3.8)	1.000	5.05%
Carfilzomib	27 (9.5)	8 (7.5)	.662	8 (7.7)	8 (7.7)	1.000	0.00%

Values are expressed as number (%) or mean±standard deviation.

BMI=body mass index, CAD=coronary artery disease, CHF=congestive heart failure, COPD=chronic obstructive pulmonary disease, PBSCT=peripheral blood stem cell transplantation, PH=pulmonary hypertension, R-ISS=revised International Staging System, VTE=venous thromboembolism.

Table 2**Laboratory findings.**

Variable	Non-PH (N = 283)	PH (N = 107)	P value
WBC (10 ³ /L)	12.7 ± 23.8	9.4 ± 6.3	.040
Hemoglobin (g/dL)	11.7 ± 1.4	11.4 ± 1.3	.062
Platelet (10 ³ /L)	300.3 ± 604.4	228.2 ± 178.3	.083
Total protein (g/dL)	8.6 ± 2.2	8.8 ± 2.3	.314
Albumin (g/dL)	3.8 ± 0.7	3.8 ± 0.6	.737
LDH (IU/L)	902.8 ± 1,302.6	1253.4 ± 2,151.8	.128
BUN (mg/dL)	36.9 ± 26.7	40.7 ± 25.8	.212
eGFR-MDRD (mL/min/1.73 m ²)	51.0 ± 31.1	43.7 ± 27.6	.039
Serum Ig G (mg/dL)	3,477.2 ± 3,117.0	3,211.1 ± 3,238.0	.555
Serum Ig A (mg/dL)	741.6 ± 1,585.6	1,489.6 ± 2,472.0	.034
Serum Ig M (mg/dL)	128.7 ± 626.2	60.8 ± 283.3	.315
Serum Ig E (mg/dL)	118.7 ± 487.8	314.4 ± 1,655.3	.393
Serum Kappa (mg/L)	918.3 ± 4,470.9	1,489.6 ± 6,013.2	.449
Serum Lambda (mg/L)	726.8 ± 2,523.2	867.2 ± 3,017.6	.699
Serum Kappa/Lambda ratio	96.6 ± 361.9	174.4 ± 841.2	.448
Serum β2 microglobulin (ug/L)	8,699.6 ± 9,994.2	9,791.3 ± 10,373.7	.449

Values are expressed as mean ± standard deviation or number (%).

BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, Ig = immunoglobulin, LDH = lactic acid dehydrogenase, MDRD = modification of diet in renal disease, WBC = white blood cell.

3.2. TTE characteristics

In terms of the TTE characteristics, the LVEDD, LVESD, and LAD were significantly greater in the PH group than in the non-PH group (Table 3). The LVEF was significantly lower and the E and A wave velocity, and E/E' ratio were higher in the PH group

Table 3**Transthoracic echocardiographic characteristics.**

Variable	Non-PH (N = 283)	PH (N = 107)	P
LVEDD (mm)	48.7 ± 4.8	51.1 ± 5.5	<.001
LVESD (mm)	31.1 ± 5.0	33.7 ± 6.4	<.001
IVSD (mm)	9.08 ± 1.86	9.23 ± 1.57	.422
LVPWD (mm)	9.60 ± 2.05	9.68 ± 1.89	.755
LAD (mm)	36.6 ± 5.8	39.8 ± 6.6	<.001
LVEF (%)	65.4 ± 6.9	62.6 ± 10.3	.010
GLS (%) [*]	-18.5 ± 4.5	-18.5 ± 4.4	.940
Mitral valve peak velocity			
E wave (m/s)	0.77 ± 0.23	0.94 ± 0.30	<.001
A wave (m/s)	0.91 ± 0.23	0.96 ± 0.25	.046
E/A ratio	0.93 ± 0.51	1.06 ± 0.66	.100
DT (ms)	207.0 ± 58.0	195.7 ± 42.7	.063
Mitral annular velocity			
Septal E' wave (m/s)	0.064 ± 0.022	0.063 ± 0.021	.660
Septal A' wave (m/s)	0.101 ± 0.029	0.109 ± 0.092	.416
E/E' ratio	12.7 ± 5.2	16.2 ± 6.8	<.001
TRV (m/s)	2.4 ± 0.3	3.1 ± 0.3	<.001
RVSP (mmHg)	32.1 ± 5.0	48.8 ± 8.2	<.001
Diastolic dysfunction			.023
Grade 1 (%)	129 (49.4)	31 (32.9)	
Grade 2 (%)	106 (40.6)	50 (53.2)	
Grade 3 (%)	26 (9.9)	13 (13.8)	

Values are expressed as mean ± standard deviation or number (%).

A wave = late diastolic velocity of mitral inflow; A' wave = late diastolic velocity of mitral septal annulus, DT = deceleration time of mitral inflow, E wave = early diastolic velocity of mitral inflow, E' wave = Early diastolic velocity of mitral septal annulus, GLS = global longitudinal strain, IVSD = interventricular septum diameter, LAD = left atrial diameter, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVPWD = left ventricular posterior wall thickness diameter, RVSP = right ventricular systolic pressure, TRV = tricuspid regurgitation velocity.

* GLS N = 139.

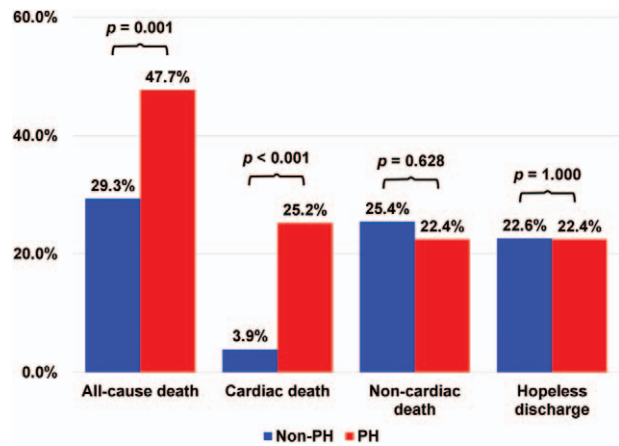


Figure 1. Incidence of the clinical outcomes according to the presence of pulmonary hypertension (PH). All-cause and cardiovascular death rates were significantly higher in the PH group than in the non-PH group, but neither non-cardiovascular death nor hopeless discharge rates were significantly different between the groups.

than in the non-PH group. A higher prevalence of increasing severity diastolic dysfunction was observed in the PH group ($P = .023$).

3.3. Clinical outcomes

During a median follow-up duration of 688 days (quartile 1 to 3: 209 to 1,316 days), all-cause death was noted for 134 patients (34.4%), and 38 patients (9.7%) died from cardiovascular causes (including ADHF, MI, and sudden cardiac arrest). All-cause and cardiovascular death rates were significantly higher in the PH group than in the non-PH group (47.7% vs 29.3%, $P = .001$; 25.2% vs 3.9%, $P < .001$, respectively), but neither non-cardiovascular death nor hopeless discharge rates were significantly different between the groups (22.4% vs 25.4%, $P = 0.628$; 22.4% vs 22.6%, $P = 1.000$, respectively; Fig. 1). In the Kaplan-Meier survival curve analysis, the PH group showed a significant association with increased all-cause and cardiovascular death rates compared to the non-PH group during clinical follow-up (Fig. 2).

3.4. Independent predictors of clinical outcomes

Table 4 showed that TTE-defined PH was a significant predictor of all-cause death [propensity score-adjusted hazard ratio [HR_{PS-adjusted}], 1.91; 95% confidence interval (CI), 1.24 to 2.95; $P = .003$], which was mainly attributable to an increased risk of cardiovascular death (HR_{PS-adjusted} 6.18; 95% CI, 2.45 to 15.61; $P = .001$). Previous history of CHF and DM were also independent predictors of all-cause death, but a history of CHF was the only independent predictor of cardiac death.

4. Discussion

We investigated the impact of TTE-defined PH at diagnosis on the future clinical outcomes in patients with. The principal findings of the present study were as follows:

- (1) During the initial work-up for the patients with MM, TTE-defined PH was observed in 107 patients (27%) and older age, lower LVEF, a greater LAD, increased E/E' ratio, and

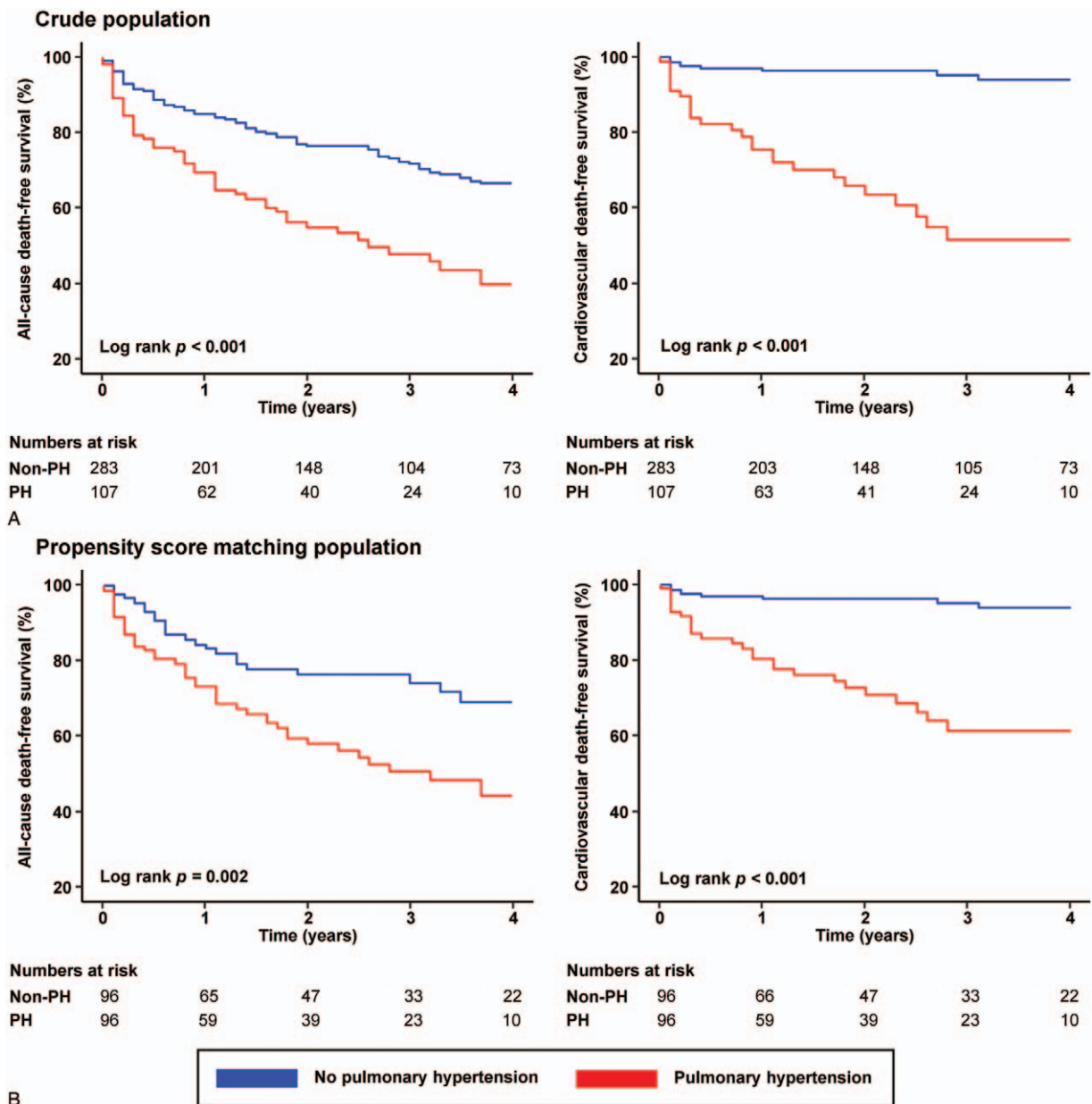


Figure 2. Kaplan-Meier curves for all-cause death and cardiovascular death between the non-pulmonary hypertension (non-PH) and PH group in the crude population (A) and propensity score-matched population (B). The PH group showed a significant association with increased all-cause and cardiovascular death rates compared to the non-PH group during clinical follow-up.

higher prevalence of increasing severity diastolic dysfunction was associated TTE-defined PH;

- (2) TTE-defined PH and a history of CHF were predictors of all-cause and cardiac death;
- (3) DM was an independent predictor of all-cause death in patients with MM.

4.1. TTE-defined PH in patients with MM

In the general population cohort, the prevalence of TTE-defined PH was approximately 2.6% to 9%.^[20,21] In a previous single-center study, 32% (N=39/123) of the patients with MM had TTE-defined PH.^[22] In our study, 27% of the patients with MM had TTE-defined PH, and serum IgA levels were higher in the PH

group than in the non-PH group ($1,396.2 \pm 2,470.3$ vs $741.6 \pm 1,585.6$ mg/dL, $P = .043$). Mestecky et al showed that moderate relative serum viscosity is common in IgA myeloma, which is associated with high serum concentrations of IgA polymer.^[23] The increase in the levels of procoagulant factors may also reflect an inflammatory reaction. A high incidence of acquired activated protein C resistance in patients with MM was observed, which disappeared during treatment and was associated with an increased risk of pulmonary embolism.^[24] The proposed mechanisms include procoagulant antibody formation, increased blood viscosity, and interference with fibrin.^[25] This result suggests that vasoactive mediators released by neoplastic cells, in addition to increased plasma viscosity, may play a role in the pathogenesis of PH in patients with MM.

Table 4
Independent predictors identified using multivariate Cox proportional hazards regression analysis.

	Crude Population		PSM Population	
	HR (95% CI)	P value	HR (95% CI)	P value
All-cause death				
Age ≥ 65 years	1.39 (0.95–2.02)	.086	1.51 (0.95–2.40)	.081
Hypertension	1.23 (0.86–1.77)	.264	1.23 (0.81–1.90)	.349
Diabetes mellitus	1.87 (1.26–2.76)	.002	2.29 (1.41–3.70)	.001
History of CHF	2.26 (1.39–3.65)	.001	2.92 (1.69–5.05)	.001
History of CAD	1.74 (0.88–3.42)	.109	1.66 (0.73–3.75)	.225
eGFR < 60 mL/min	1.80 (1.19–2.70)	.005	1.51 (0.93–2.46)	.094
IgA > 500 mg/dL	1.01 (0.69–1.44)	.985	1.22 (0.78–1.91)	.377
RVSP > 40 mmHg	1.94 (1.34–2.81)	<.001	1.91 (1.24–2.95)	.003
LAD > 40 mm	1.18 (0.80–1.74)	.404	1.01 (0.62–1.62)	.996
E/E' > 14	1.03 (0.71–1.51)	.863	1.07 (0.68–1.68)	.772
EF < 50%	2.30 (1.22–4.35)	.010	1.96 (0.63–6.10)	.243
Cardiovascular death				
Age ≥ 65 years	1.56 (0.75–3.27)	.236	1.31 (0.51–3.36)	.577
Hypertension	0.98 (0.49–1.96)	.950	0.82 (0.34–2.00)	.660
Diabetes mellitus	1.22 (0.53–2.81)	.644	1.81 (0.67–4.89)	.243
History of CHF	3.33 (1.45–7.68)	.005	6.40 (2.31–17.74)	.001
History of CAD	1.46 (0.42–5.10)	.554	0.77 (0.09–6.19)	.803
eGFR < 60 mL/min	1.57 (0.66–3.74)	.306	1.35 (0.51–3.61)	.544
IgA > 500 mg/dL	1.01 (0.45–1.85)	.806	1.38 (0.57–3.36)	.480
RVSP > 40 mmHg	6.68 (3.14–14.21)	<.001	6.18 (2.45–15.61)	.001
LAD > 40 mm	1.79 (0.89–3.59)	.102	1.45 (0.60–3.50)	.404
E/E' > 14	1.17 (0.55–2.48)	.679	0.98 (0.40–2.41)	.961
EF < 50%	4.19 (1.70–10.31)	.002	0.76 (0.07–8.33)	.823

Abbreviations are as in Tables 1–3.

CI = confidence interval, HR = hazard ratio, PSM = propensity score-matched.

4.2. TTE-defined PH and CHF

In the present analysis, TTE-defined PH (RVSP > 40 mmHg) and a history of CHF were the independent prognostic factors for all-cause and cardiovascular death in patients with MM. A previous study reported that the development and severity of PH in CHF were associated with increased mortality and morbidity, and RVSP was shown to be a strong predictor of mortality even after adjusting for diastolic dysfunction.^[26] In our study, a history of CHF was an important prognostic factor, suggesting that additional precapillary components may have contributed to the development of PH. In addition, we found a greater LAD, increased E/E' ratio, and higher prevalence of increasing severity diastolic dysfunction in the PH group. This is not simply attributable to an increase in the filling pressure on the left side and may also be partly due to active pre-capillary components, as revealed by an increased transpulmonary pressure gradient. Pathologically, pulmonary capillary remodeling, such as medial hypertrophy and muscularization, plays an important role in longstanding PH due to CHF.^[27]

4.3. DM and MM

In our study, DM was an independent prognostic factor for all-cause death in the propensity-matched population. In a previous retrospective study, DM, steroid-induced DM in particular, was associated with poor clinical outcomes in MM.^[28] MM cells express high levels of insulin receptor (IR) and insulin-like growth factor 1 receptor (IGF-1R), and insulin stimulates their growth through IR/IGF-1R hybrid receptor activation.^[29] Activation of the IR/IGF-1R signaling pathway may result in dexamethasone resistance in myeloma cells.^[30] Thus, the theory that endogenous

and exogenous insulin and its analogs promote the growth of malignant cells and chemo-resistance seems to be an appropriate explanation for this finding in our study.

This is the first study to show that TTE-defined PH and CHF are an independent poor prognostic factor in multiple myeloma patients. Taken together, it is necessary to identify the underlying cause of PH because the treatment direction may differ accordingly. In the available literature, left heart disease is the most common cause of PH in the normal population^[20]; however, right heart catheterization is necessary for the differential diagnosis in patients with MM due to the presence of thrombophilia and hyperviscosity.

The main limitation of the present study is that the TTE findings cannot clearly identify the causal mechanisms of PH, which requires right heart catheterization and formal clinical evaluation. Second, it was a retrospective single-center observational study and included a relatively small number of patients. A large prospective cohort study is needed to determine whether each factor affects pulmonary hypertension. Third, we found no association of PH with pulmonary venous thromboembolism (4.6% vs 1.9%, $/p = .340$); however, this may be underestimated since patients with MM often have impaired renal function (eGFR, 51.0 ± 31.1 vs 43.7 ± 27.6 mL/min/1.73 m²; $P = .039$) and are hesitant to receive enhanced CT (PH group $n = 22$ (20.6%) vs non-PH group $n = 99$ (35.0%), $P = .009$). Therefore, when PH in TTE is present, it is necessary to distinguish PTE through ventilation/perfusion lung scan that do not affect kidney function. Fourth, the duration of PH and follow-up for the degree of improvement were not investigated in the present study. Certainly, the presence of PH may influence the long-term mortality rates, but mortality associated with the improvement of

PH is also likely to be important. No studies have shown the difference between improvement in PH and prognosis after treatment of multiple myeloma. So, further studies are needed. Fifth, the Doppler derivative pressure estimation may have been inaccurate in individual patients. Furthermore, since the transpulmonary pressure gradient may be highly underestimated and cannot be used to exclude PH, the pressure may also have been overestimated.^[15] Finally, we adjusted for multiple confounding factors using the multivariable Cox regression model and propensity score matching; however, we cannot exclude the possibility of potential unknown confounding factors. Therefore, larger studies are needed to investigate the impact of PH in patients with MM.

5. Conclusions

This study demonstrates that the prevalence of TTE-defined PH is higher in patients with MM than in the general population. Moreover, TTE-defined PH and a history of CHF are the independent prognostic factors for all-cause and cardiovascular death in patients with MM. These results highlight the risk of associated cardiovascular disease in patients with MM and emphasize the importance of management strategies that prevent the deterioration of cardiac function.

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