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ORIGINAL ARTICLE

Resistant Hypertension and Related Outcomes in a Cohort of Patients with Cardiorenal Multimorbidity Hospitalized in an Internal Medicine Ward

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Abstract

Introduction Resistant hypertension (RH) is characterized by the failure to reach a goal blood pressure despite the administration of three medications at maximally tolerated doses, one of which being a diuretic. RH can be observed in a variety of clinical conditions, such as heart failure and reduced renal function and may confer high cardiovascular risk.

Aim To evaluate the prevalence of RH and its association with clinical outcomes; the primary outcome was in-hospital mortality and the composite outcome was all-cause of mortality and morbidity in a cohort of patients with cardiorenal multimorbidity hospitalized in an internal medicine ward.

Methods We conducted a retrospective analysis of consecutive hypertensive patients with cardiorenal multimorbidity. The composite outcome incorporated all-cause of in-hospital mortality and occurrence of sepsis, pulmonary embolism, acute coronary syndrome, stroke and renal replacement therapy.

Results We collected data in 141 inpatients with a mean age of 77 years ± 10 (males 65.9 %), estimated glomerular filtration rate of 34 ± 18.6 ml/min with length of stay of 17 ± 12 days. The prevalence of RH was 52.4%. In-hospital mortality was observed in 24 patients (17%) and the composite outcome occurred in 87 patients (61.7%) and among these 74 (85.1%) were patients with RH. Free survival for composite outcome was significantly higher in patients without RH than patients with RH (log rank 7.52, p = 0.006).

Resistant hypertension was a risk factor for composite outcome [HR 1.857(C.I. 1.170–2.946, p = 0.009)].

Conclusion In patients with cardiorenal multimorbidity there is a high proportion of RH that represents a risk factor for composite outcome but not for in-hospital mortality.

Keywords Resistant hypertension · Cardiorenal multimorbidity · Heart failure · Chronic kidney disease

1 Introduction

Resistant hypertension (RH) is a clinical condition characterized by the failure to reach a goal blood pressure (BP) despite the administration of three medications with complementary mechanisms at maximally tolerated doses, one of which being a diuretic. The real worldwide prevalence of RH is difficult to assess because it is related to several factors among which method of BP measurement, antihypertensive drugs prescribed, target BP to achieve in different clinical setting, adherence to treatment and features of enrolled patients [1]. In the literature RH prevalence ranges 5% to 30% [2, 3] among all hypertensive patients, with a more likely prevalence of 10.3% as described by a recent meta-analysis which reported 91 studies published over a 26 year period [4]. However, the percentages changed when several and specific subgroups were considered reaching up to 22.9% and 56% in chronic kidney disease (CKD) and renal transplant, respectively [4].

The associated risk factors are advanced age, male sex, African ethnicity, type II diabetes mellitus (DM), alcohol

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intake, high sodium intake and other factors related to hypertensive history (systolic BP levels at the time of diagnosis, failure to reach normal BP during follow-up, delayed diagnosis).

Resistant hypertension can be observed in a variety of clinical conditions, such as heart failure (HF), CKD or both and may confer high cardiovascular risk [5, 6].

In response to the ageing population, there has been an increase in prevalence of cardiovascular and renal diseases, which share common pathophysiological mechanisms and risk factors. The co-presence of these conditions, known as cardiorenal multimorbidity (CRM), has gained more and more interest in clinical management, considering the association with worse clinical outcomes and the need of new therapeutical strategies [7].

Aim of this retrospective study was to evaluate the prevalence of RH and its association with clinical outcomes; the primary outcome was in-hospital mortality and the composite outcome was all-cause of mortality and morbidity in a cohort of patients with CRM hospitalized in an internal medicine ward.

2 Methods

2.1 Study population

We conducted a cross-sectional study in a cohort of patients with CRM hospitalized in an internal medicine ward in three consecutive years before the COVID-19 pandemic outbreak. The study was conducted in accordance with the Declaration of Helsinki. All the patients have received and signed the informed consent. The study project was approved by the Local Ethics Committee.

From the clinical records we collected information including personal data, all comorbidities and diseases during hospitalization, biochemical analyses, length of stay (LOS) and death.

Chronic kidney disease was diagnosed according to K-DOQI (Kidney Disease Outcomes Quality Initiatives) guidelines [8]. Renal function was evaluated by the estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) expressed as a single equation: GFR = 141 × min (sCr/k, 1) α × max (sCr/k, 1) − 1.209 × 0.993 age × 1.018 (if female) × 1.159 (if black), where k is 0.7 for females and 0.9 for males, α is − 0.329 for females and − 0.411 for males, min indicates the minimum of sCr/k or 1, and max indicates the maximum of sCr/k or 1 [9]. Coronary artery disease (CAD) was diagnosed based on American College of Cardiology/American Heart Association guidelines [10]. Heart failure was defined according to European Society of Cardiology (ESC) guidelines [11]. Resistant hypertension was defined in accordance with the 2023 ESH/ESC guidelines [1].

2.1.1 Outcome definition

The primary outcome was in-hospital mortality and the composite outcome incorporated all-cause of in-hospital mortality and occurrence of sepsis, pulmonary embolism, acute coronary syndrome, stroke and renal replacement therapy.

2.2 Statistical analysis

The coefficient of Kurtosis was used to evaluate normal distribution of data. All the results are expressed as mean ± standard deviation (SD) or absolute frequency and percentage. Group comparisons were made by Student's t-test or Mann–Whitney test, as appropriate. The chi-square test or Fisher's exact test, as appropriate, were used to compare categorical variables. Cox regression analysis with Hazard Ratio (HR) and 95% confidence intervals (CI) were applied to evaluate the predictive role of independent variables for in-hospital mortality and for composite outcome. Kaplan–Meier curves with the log-rank test were used to evaluate free survival from composite outcome in patients with or without RH.

The calculation for the determination of sample size calculation was based on the prevalence of RH (confidence level of 99% and confidence interval of 10%) which recommended sample size of 130 patients. p values <0.05 were considered significant. SPSS version 26.0 software was used for statistical analysis.

3 Results

Demographic and clinical features of patients enrolled are shown in Table 1.

We collected data of 141 inpatients (males 65.9%) with a mean age of 77 ± 10 years eGFR of 34 ± 18.6 ml/min with LOS of 17 ± 12 days. The prevalence of RH in our cohort of CRM patients was 52.4%. In-hospital mortality was observed in 24 patients (17%) and the composite outcome occurred in 87 patients (61.7%) and among these 74 (85.1%) were patients with RH. Mean age of RH patients and patients without RH was similar (77 ± 9 years vs 77 ± 11 years, p > 0.05). Moreover, RH patients had a similar LOS compared to patients without RH (18 ± 13 days vs 16 ± 12 days, p > 0.05). There was no statistically significant difference in sex distribution between RH patients and patients without RH, with a prevalence of male sex in both groups [48 (34%) vs 45 (31.9%), p > 0.05].

Although not statistically significant, there was a trend in the association between age and in-hospital mortality [HR

Table 1 Demographic and clinical features of 141 patients enrolled

Age, years, mean ± SD	77 ± 10
M/F, n (%)	93 (65.9) / 48 (34.1)
Lenght of stay, days, mean ± SD	17 ± 12
Serum creatinine, mg/dl, mean ± SD	2.46 ± 1.78
eGFR, ml/min, mean ± SD	34 ± 18.6
Resitant hypertension, n (%)	74 (52.5)
Atrial fibrillation	
Chronic, n (%)	34 (24.1)
Paroxysmal, n (%)	21 (14.9)
Coronary artery disease, n (%)	84 (59.6)
Heart failure, n (%)	47 (33.3)
Diabetes mellitus, n (%)	58 (41.1)
Dyslipidemia, n (%)	10 (7.1)
Nephrotic syndrome, n (%)	6 (4.2)
Kidney injury	
Acute, n (%)	74 (52.5)
Chronic III–IV stage, n (%)	34 (24.1)
Chronic V stage, n (%)	11 (7.8)
Chronic obstructive pulmonary disease, n (%)	39 (27.6)
Pulmonary embolism, n (%)	1 (0.7)
Deep vein thrombosis, n (%)	1 (0.7)
Arterial disease, n (%)	79 (56)
Cerebrovascular disease, n (%)	46 (32.6)
Liver failure, n (%)	11 (7.8)
Cancer, n (%)	12 (8.5)
Infectious disease	
Sepsis, n (%)	9 (6.4)
Pneumonia, n (%)	15 (10.6)
Urinary tract infection, n (%)	47 (33.3)
Exitus, n (%)	24 (17)
Composite outcome, n (%)	87 (61.7)

All data are reported as mean ± standard deviation or absolute frequency and percentage

SD standard deviation, *eGFR* estimated glomerular filtration rate

1.044 (95% CI 0.998–1.092, p = 0.059)] and CAD [HR 0.414 (95% CI 0.162–1.057, p = 0.065)].

Sex [HR 1.065 (95% CI 0.460–2.468, p = 0.883)], type II diabetes mellitus [HR 1.837 (95% CI 0.722–4.673, p = 0.202)], chronic obstructive pulmonary disease [HR 0.679 (95% CI 0.292–1.580, p = 0.369)], atrial fibrillation [HR 0.435 (95% CI 0.176–1.074, p = 0.071)], kidney disease [HR 0.445 (95% CI 0.174–1.136, p = 0.090)] and RH [HR 0.741 (95% CI 0.326–1.683, p = 0.473)] did not show any association with in-hospital mortality (Table 2).

Resistant hypertension was a risk factor for composite outcome [HR 1.857 (95% CI 1.170–2.946, p = 0.009)], while no significant association was found with age [HR 1.008 (95% CI 0.988–1.029, p = 0.425)], sex [HR 0.917 (95% CI 0.589–1.427, p = 0.701)], diabetes [HR 0.889 (95% CI 0.578-1.366, p = 0.590)] and chronic obstructive pulmonary disease [HR 0.883 (95% CI 0.561–1.389, p = 0.591)]. Cox regression analysis for composite outcome is summarized in Table 3.

Table 2 Cox regression analysis with hazard ratio (HR) and 95% confidence interval (CI) for exitus

	HR (CI)	p
Age	1.044 (0.998–1.092)	0.059
Sex	1.065 (0.460–2.468)	0.883
Resistant hypertension	0.741 (0.326–1.683)	0.473
Atrial fibrillation	0.435 (0.176–1.074)	0.071
Diabetes mellitus	1.837 (0.722–4.673)	0.202
Coronary artery disease	0.414 (0.162–1.057)	0.065
Chronic obstructive pulmonary disease	0.679 (0.292–1.580)	0.369
Kidney disease	0.445 (0.174–1.136)	0.090

Free survival for composite outcome was significantly higher in patients without RH than patients with RH (log rank 7.52, p = 0.006) (Fig. 1).

4 Discussion

The present observational retrospective study suggest that RH represents a predictive risk factor for composite outcome in patients with CRM. It is well known that RH is significantly associated with increased major cardiovascular events [12], end stage renal disease and all-cause mortality and represents a recognized burden for economical/health system [13, 14].

Of note, in the cohort studied, the prevalence of RH was 52.5%, thus higher than described in the overall hypertensive population [1]. The higher prevalence observed in the present study could be partially explained by the underlying disease burden that can be caused or complicated by hypertension in hospitalized patients, such as CKD and HF.

The prevalence of RH in patients affected by CKD ranges from 15.8 to 33.4%, according to the CKD stage [15], with an average value of 22.9% [3] and up to 48.3% when patients

Table 3 Cox regression analysis with hazard ratio (HR) and 95% confidence interval (CI) for composite outcome

	HR (CI)	p
Age	1.008 (0.988–1.029)	0.425
Sex	0.917 (0.589–1.427)	0.701
Resistant hypertension	1.857 (1.170–2.946)	0.009
Diabetes mellitus	0.889 (0.578–1.366)	0.590
Chronic obstructive pulmonary disease	0.883 (0.561–1.389)	0.591

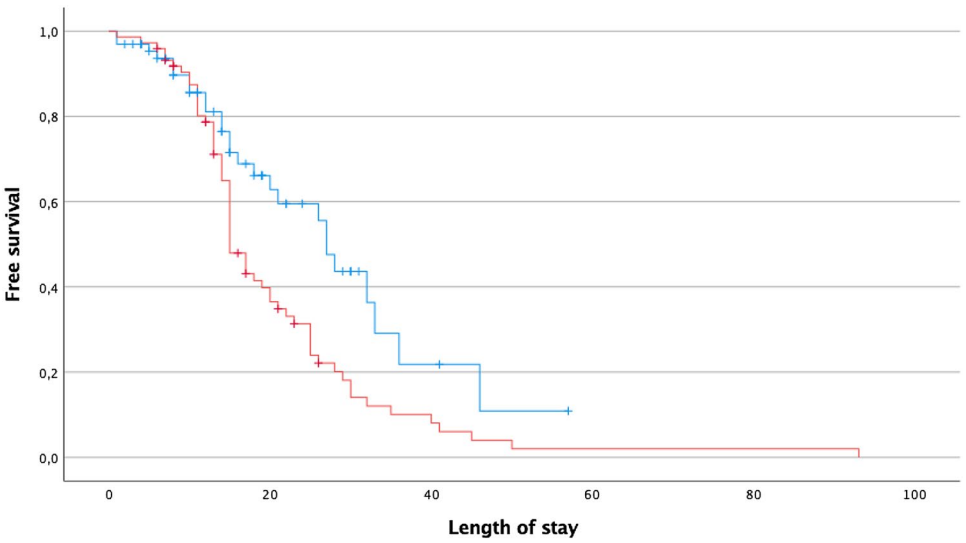

Fig. 1 Kaplan–Meier curves for composite outcome in patients with (red line) or without (blue line) resistant hypertension

with RH were classified according to the albumin-creatinine ratio [16]. In patients with HF and CAD the prevalence ranges from 13.7 to 21.8%, respectively [17, 18].

Literature data suggest that, in general population, individuals with RH are at greater risk for renal failure in addition to cardiovascular events [14]. The relationship between heart and kidney is critical for maintaining physiological hemodynamic and perfusion homeostasis, but the crosstalk becomes a double-edged sword in pathological conditions in which dysfunction of one organ promotes functional and/or structural alteration of the other [19]. According to this synergistic interaction, both CKD and HF share same pathophysiological mechanisms, such as sodium and water retention with consequent volume overload, vascular dysfunction, increased activity of the renin-angiotensin-aldosterone and sympathetic nervous systems [20]. Considering these shared pathophysiological mechanisms and the use of the same pharmacological strategies, among which antihypertensive drugs and diuretics, a higher RH prevalence in our study with respect to literature is not surprising [2, 3, 5–7].

Although the analysis of our data did not show an association between in-hospital mortality or LOS and RH, we observed a statistically significant association between RH and the composite outcome of morbidity and mortality. Also, we described a significantly higher free survival in patients without RH, than patients with RH.

The worst prognosis of RH patients with respect to non-RH patients is documented in previous studies and explained by structural and functional cardiac and renal changes, such as left ventricular hypertrophy, increased aortic stiffness, atherosclerotic plaques and microvascular disease. These changes, moreover, promote and further worsen hypertension creating a self-sustaining mechanism [21]. Of interest, in the present study we highlighted for the first time an association between f RH and worse prognosis, specifically in a cohort of in-patients affected by CRM. These data suggest that RH patients deserve more clinical attention and early therapeutic optimization in specialized centers, to improve clinical outcomes and *quoad vitam* prognosis.

In the last decade, the importance of adequately recognizing and early treating of RH patients conferred more interest on the research of innovative device-based therapies such as renal denervation (RDN) [1, 22]. The RDN represents an alternative treatment, in patients with an eGFR >40 ml/min/1.73 m^2, able to modulate the overactive pathway between the kidneys and the central nervous system, mainly responsible for the trigger in RH [23, 24].

However, there is still no clear position on RDN recommendation and it is obviously not free from procedural risks. Furthermore, a significant reduction in cardiovascular events over long-term follow-up after RDN is not studied yet [21, 23–25].

Finally, it should be remembered that the modification of lifestyle always represents the first line intervention for the hypertension management. Data suggest that a physical exercise program, besides the medical therapy alone, is effective at lowering the ambulatory BP (till a reduction of at least 5 mmHg) [26].

5 Limitations

The study has some limitations, first it is a retrospective and monocentric. Second, not all causes of pseudo-resistant hypertension among which "white coat hypertension" or causes of secondary hypertension were completely excluded.

The study, however, has some strengths due to adherence to therapy. The cohort of patients analyzed were inpatients, in whom therapy was prescribed and administered correctly,

excluding at least one of the most frequent causes of pseudo-resistant hypertension.

6 Conclusion

In conclusion, RH is a frequent condition in Internal Medicine Wards with a worse prognosis in patients with CRM. The RH is a predictive risk factor for composite outcome in patients with CRM beside worsening cardiovascular risk.

Declarations

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Conflict of interest No conflict of interest to declare.

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