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The aging burden of hospitalization for heart failure in Chinese populations: evidence from the Macao Heart Failure Study

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Abstract

Objective To assess the aging burden of hospitalization for heart failure in Chinese populations in Macao. **Methods** The Macao Heart Failure Study consists of patients hospitalized with a diagnosis of acute heart failure (AHF) at Centro Hospitalar Conde de São Januário (the only public hospital that provides medical care for the approximately 600,000 residents of Macao) from January 2014 to December 2016. First, we investigated the relationship between socioeconomic development and epidemiological characteristics of HF in Macao. Then we assessed the patients' clinical features and outcomes according to the age groups. **Results** A total of 967 patients were included in the final analysis. The median age at admission was 82 years old. The advanced age at the admission of HF in Macao was significantly associated with a high-income level and the aging population structure. Marked heterogeneity existed in the epidemiological characteristics, clinical features, utilization of evidence-based therapies, short- and long-term outcomes, and prognostic utility of clinical variables among the different age groups. **Conclusion** Rapid economic development and significantly aging populations have produced a profound impact on the epidemiological characteristics of HF in Chinese populations. Acute decompensated heart failure (ADHF) is predominantly a disease of the elderly in Macao, and a significant heterogeneity exists in the clinical features, managements, and outcomes among different age groups. Age-based risk stratification models and multidisciplinary HF teams are urgently needed to improve the management and outcomes of hospitalized heart failure (HHF) patients.

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1 Introduction

As is generally recognized, heart failure (HF) is an emerging epidemic that affects approximately 3% of the adult population (approximately 28 million people worldwide).[1,2] Current literature in Western countries has shown a significant increase in the incidence and prevalence of HF partially due to the growth of the aging population.[3,4] Acute heart failure (AHF) has become a prevalent disease of older populations in Western countries. The results of a large multinational cohort of patients hospitalized with heart failure (HHF) demonstrated that the clinical characteristics, management states, and outcomes varied significantly among different age groups.[5] The current comprehensive information regarding elderly HF patients was mainly derived from Europe and North America, while studies from developing economies, especially China, remain scarce.

Macao is a suitable model for understanding HF development trends in Chinese populations as society ages. As a special administrative region of China, Macao underwent rapid urbanization several decades earlier than Mainland China. The associated Westernization of local lifestyles and modernization of the health care system in Macao have led to a significant increase in life expectancy and a high prevalence of HF in the elderly. The hospital-based registry in Macao may provide important evidence to formulate effective quality improvement initiatives for Chinese HF patients in the future, particularly for the elderly.

The main aims of the present study were to assess the aging burden of HHF in a Chinese population in Macao, (1)

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the relationship between socioeconomic development and epidemiological characteristics of HF in Macao; (2) demographic characteristics, clinical features, management, and outcomes among different age groups; and (3) prognostic indicators of short- and long-term outcomes according to age groups.

2 Methods

2.1 Study population

Centro Hospitalar Conde de São Januário is the only public hospital that provides medical care for the approximately 600,000 residents of Macao. Consecutive patients with a principal discharge diagnosis of AHF at Centro Hospitalar Conde de São Januário from January 2014 to December 2016 were identified. The diagnostic criteria of AHF were according to either the 9th or 10th revision of the International Classification of Diseases (ICD-9 or ICD-10). Patients with *de novo* HF and those with decompensated chronic HF were included.

This study complied with the Declaration of Helsinki, that the local institutional ethics committee has approved the research protocol and that informed consent has been obtained from the subject. Before the launch of the Macao Heart Failure Study, information on the objectives of the present study, its social significance, and an abstract were provided for clinical trial registration with the Chinese Clinical Trial Registry (ChiCTR2000032613).

Qualified discharged patients had to meet the following criteria: (1) Chinese population; (2) all questions on the electronic case report form completed; (3) all data queries successfully answered by the hospital's research coordinator; and (4) patients who signed the informed consent. Cases were excluded for any of the following reasons: (1) patient younger than 18 years of age; (2) patient did not have ADHF during the index hospitalization; (3) medical records not retrievable; or (4) lost to follow-up.

2.2 Study design

This project was a retrospective cohort study based on the hospitalized HF registry. Clinical information on individuals including (1) age and gender; (2) symptoms, physical signs, and vital signs at presentation; (3) medical conditions diagnosed before or during the index hospitalization, including hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), myocardial infarction, peripheral arterial disease, atrial fibrillation/flutter (Af/AF), ischemic stroke/transient ischemic attack, hypertrophic cardiomyopathy, congenital heart disease, and myocarditis; (4) echocardiogram findings conducted during index hospitalization; (5) results of blood tests including creatine and electrolytes; and (6) medication at admission and discharge.

All the patients in this cohort were followed up in our public health system. Clinical outcomes, including deaths and readmissions, were retrieved from the computerized medical records. The primary outcome was all-cause mortality during the follow-up period. The secondary outcomes were deaths from cardiovascular causes and readmissions for HF.

Considering the possible impact of socioeconomic factors on the admitted age of HF, we investigated the relationship between the median/average age of HF and the economic level (GDP per capita) in representative HHF registries.[6–19] In addition, we further analyzed the relationship between admitted age of HF[6–18] and demographic structure (the degree of social aging measured by the percentage of the population aged 65 or older) in the same period in these countries and regions.[20]

2.3 Statistical analysis

The results were expressed as median and first to third quartile or number and percentage. The group used as a reference in the model was the young patient group (age younger than 65 years). We divided the definition of the elderly into three age groups to account for its diversity: the ‘middle-old’ aged 65–74 years, the ‘old-old’ aged 75–84 years, and the ‘oldest-old’ aged 85 years old and older. Differences between groups were tested using the chi-squared test or Kruskal-Wallis test as appropriate. Linear regression analysis was used to assess the correlation between two sets of continuous variables. We used a Cox proportional hazard model to test the mortality risk prediction. Clinical variables used to adjust age groups in the full model for the mortality risk prediction were gender, comorbidities (history of CHF, hypertension, diabetes mellitus, and atrial fibrillation/flutter), hemodynamic status at admission [systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR)], laboratory test results (creatinine and hemoglobin), hyponatremia (≤135 mmol/L), and left ventricular ejection fraction (LVEF) estimated by echocardiogram. Kaplan-Meier survival analyses with the log-rank test were used to compare the clinical outcomes of the different age groups.

Statistical analyses were conducted using SPSS software (version 20.0). All the tests were 2-sided, and $P < 0.05$ was considered statistically significant.

3 Results

Between January 2014 and December 2016, 1060 patients were admitted due to ADHF, among which 56 were non-Chinese, 10 had missing data, and 18 were lost to follow up. Ultimately, 967 patients were included in the final analysis (see Supplementary Figure S1). The median admitted age of ADHF in Macao was 82 years old, and females accounted for 50.2%.

3.1 Relationship between admitted age of HF and socioeconomic development in Macao

Compared with the data of representative HHF registries conducted in other countries and regions, the median admitted age of HF in Macao was 16 years older than in Mainland China and approximately 10 years older than in North America and Western countries.[6–17]

Linear regression analysis showed there was a significantly positive relationship between economic development level and admitted age of HF. As GDP per capita increased, the median admitted age also increased. Compared with many other developed economies, Macao has considerably high GDP per capita with a high median age of admitted HF (Figure 1A).

As depicted in Figure 1B, the age of presentation of HF was also positively correlated with the severity of population aging. In general, the median admitted age of HF was higher when the level of social aging was more severe. However, although the degree of social aging in Macao is less severe than that in a series of developed countries such as the UK and Japan, the median admitted age of HF in Macao (82 years) was markedly higher than in those regions (Japan 73.0 ± 14.0 years;[14] European countries 69.9 ± 12.5 years[8]) (Figure 1B).

3.2 Epidemiological characteristics of ADHF in Macao

As shown in Figure 2A, throughout the observation period, the proportion of the young patient group (< 65 years) was only 21.3%, while nearly one-third were classified as the oldest-old group (≥ 85 years) (33.1%) (Figure 2A).

Figure 2B depicted the incidence of HF by sex and age groups. Although the rate of HF hospitalization remained relatively low for those younger than 64, it rose steeply for both men and women older than 65. With each 10-year age increase in the patients between 65–85 years, the HF incidence rates doubled in men and tripled in women. For those aged 85 years or older, the HF incidence rate was as high as 13.01 per 1,000 population per year.

Besides, the rate of HHF in men was higher than in women in the patients younger than 84 years, while this trend reversed for those aged 85 years or older. The prevalence of HHF was significantly higher in women than in men in the oldest-old group (14.25% *vs*. 10.97%, $P < 0.001$) (Figure 2B).

3.3 Baseline clinical characteristics of overall population

The baseline characteristics of the 967 subjects are provided in Table 1. More than half of the patients were admitted to the intensive care unit (58.5%).

The most prevalent etiologies of HF included ischemic

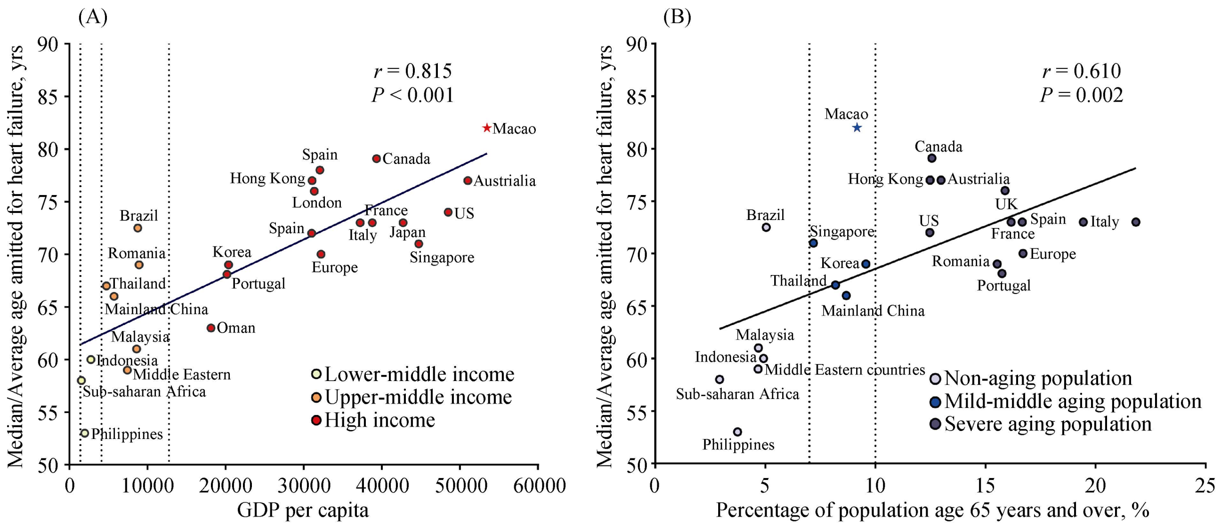

Figure 1. The relationship between the median/average age admitted for heart failure and economic level (GDP per capita) and demographic structure (the degree of social aging measured by the percentage of the population aged 65 years or over). (A): Scatterplot of the median/average age admitted for HF and GDP per capita for selected countries; and (B): scatterplot of the median age admitted for HF against the percentage of the population aged 65 and over for selected countries. The median/average age admitted for heart failure in other countries was derived from the international representative registries.[6–18] The GDP per capita and percentage of population age at 65 years and over of these countries over the same period of representative registries came from the World Bank database.[19]

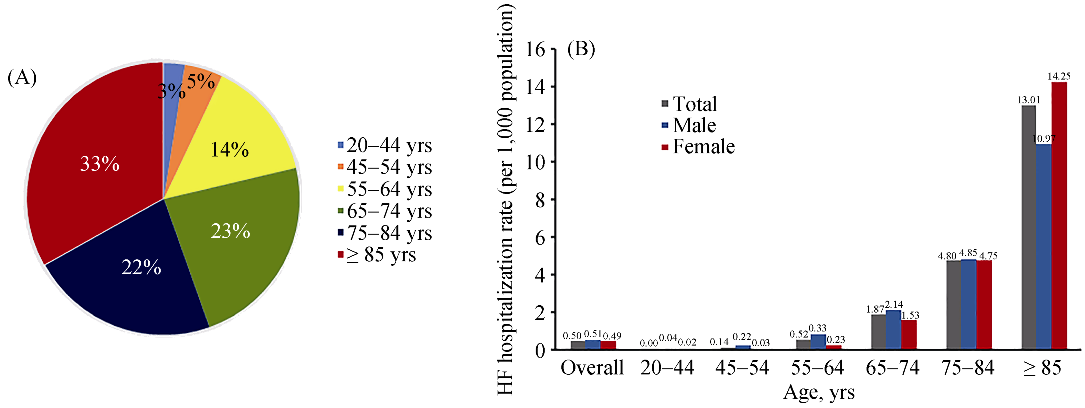

Figure 2. The age distribution and hospitalization rate of acute heart failure by age and gender in Macao. (A): age distribution of acute heart failure patients in Macao; and (B) hospitalization rate for acute heart failure in Macao by age and gender. HF: heart failure.

heart disease (42.9%), hypertensive heart disease (25.2%), and significant valvular heart disease (17.8%), whereas idiopathic dilated cardiomyopathy, congenital heart disease, and other genetic cardiomyopathy were identified only in a small proportion of patients.

The main precipitating factors of HHF in Macao was acute coronary syndrome (32.3%), followed by infection (19.8), fluid overload (17.9%), arrhythmia (17.5%), and hypertension (11.9%). The proportion of patients with poor compliance was low (4.9%).

The proportion of patients with hypertension in this cohort was as high as 85%. The patients with anemia and DM also had a significant prevalence (59.9% and 47.2%, respectively). The other comorbidities, including prior stroke/TIA, renal dysfunction, and atrial fibrillation/flutter, were present in approximately one-third of all of the patients (34.1%, 33.2%, and 32.5%, respectively). Among all of the patients, 407 (42.1%) had a previous diagnosis of HF, and 425 (48.3%) presented with LVEF less than 40% (Table 1).

3.4 Comparison of clinical characteristics among the age groups

As shown in Table 1, with increasing age, we demonstrated a predicable increase in the proportion of female patients and patients admitted to the intensive care units.

We also noted a transient increase in the prevalence of ischemic heart disease that peaked at 48.9% in the middle-old group. Comparatively, in the young patient group, the rheumatic valvular disease had a high prevalence, while in the old-old and oldest-old patient groups, degenerative valvular heart disease was more prevalent. Idiopathic dilated cardiomyopathy usually occurred in the young patient group, which was less common in the middle-old patient group, as the patients with idiopathic dilated cardiomyopathy rarely survived longer than 75 years (Table 1).

Infection-induced worsening of HF was more frequent in the elderly than in young patients, accounting for 24.7% of the precipitating hospitalization factors in the oldest-old group. Non-compliance with therapy was less common in the elderly group than in the young group (Table 1).

According to medical history, the incidences of comorbidities such as HTN, renal dysfunction, anemia, and Af/AF markedly increased with age. The prevalence of DM and CAD peaked at 56.9% and 21.8% in the middle-old group. Of note, the proportion of patients with LVEF > 40% significantly increased with age (Table 1).

3.5 Comparison of the utilization of evidence-based therapies among the age groups

As shown in Figure 3, at admission, the recommended treatments for chronic HF, including β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and mineral corticoid receptor antagonists (MRA) were insufficient for all age groups. The utilization rate of ACEI/ARB decreased from 47.1% in the young patients to less than 40% in the oldest-old patients. Those using β-blockers decreased from 56.8% in the young patient group to 36.6% in the oldest-old patient group. Similarly, the application of MRA was higher in the young patient group (35.4%) than in the oldest-old group (16.9%) (Figure 3A).

At discharge, the utilization of the evidence-based therapies was significantly increased across all the age groups. However, these recommended treatments remained less frequently used in elderly patients than those in the younger groups (Figure 3B).

3.6 In-hospital and post-discharge outcomes according to age group

Although the median length of stay (LOS) ranging from

Table 1. Baseline characteristics of study population according to age group.

Variables	Overall population (*n* = 967)	Age < 65 yrs (*n* = 206)	Age 65 to 74 yrs (*n* = 225)	Age 75 to 84 yrs (*n* = 216)	Age ≥ 85 yrs (*n* = 320)	*P*-value
Age, yrs	82.0 (66.0–88.0)	58.0 (53.0–62.0)	69.0 (67.0–72.0)	80.0 (78.0–83.0)	91.0 (88.0–96.0)	< 0.001
Female	485 (50.2%)	54 (26.2%)	93 (41.3%)	120 (55.6%)	218 (68.1%)	< 0.001
Admission location						
Intensive care unit (CCU/ICU)	566 (58.5%)	77 (37.4%)	85 (42.2%)	156 (72.2%)	240 (75.0%)	< 0.001
General ward	399 (41.3%)	129 (62.6%)	130 (57.8%)	60 (27.8%)	240 (25.0%)	
Etiology of heart failure						
Ischemic heart disease	415 (42.9%)	76 (36.9%)	110 (48.9%)	93 (43.1%)	136 (42.5%)	0.096
Hypertensive heart disease	244 (25.2%)	47 (22.8%)	44 (19.6%)	65 (26.6%)	88 (36.1%)	0.045
Valvular heart disease	172 (17.8%)	38 (18.4%)	19 (8.4%)	45 (20.8%)	70 (21.9%)	< 0.001
Idiopathic dilated cardiomyopathy	56 (5.8%)	29 (14.1%)	27 (12.0%)	0	0	< 0.001
Congenital heart disease	20 (2.1%)	13 (6.3%)	4 (1.8%)	1(0.5%)	2 (0.2%)	< 0.001
Precipitating factors						
ACS	312 (32.3%)	76 (36.9%)	82 (36.4%)	62 (28.7%)	92 (28.8%)	0.076
Arrhythmia	169 (17.5%)	24 (11.7%)	39 (17.3%)	42(19.4%)	64 (20.0%)	0.077
Hypertensive	115 (11.9%)	17 (8.3%)	20 (8.9%)	31 (14.4%)	47 (14.7%)	0.043
Infection	191 (19.8%)	28 (13.6%)	40 (17.8%)	44 (20.4%)	79 (24.7%)	0.015
Fluid overload	173 (17.9%)	42 (24.3%)	39 (22.5%)	36 (20.8%)	56 (32.4%)	0.759
Non-compliance with therapy	47 (4.9%)	18 (8.7%)	10 (4.4%)	8 (3.7%)	11(3.4%)	0.032
Medical history						
Hypertension	822 (85.0%)	139 (67.5%)	185 (82.2%)	199 (92.1%)	299 (93.4%)	< 0.001
Diabetes mellitus	456 (47.2%)	90 (43.7%)	128 (56.9%)	112 (51.9%)	126 (39.4%)	< 0.001
Prior Stroke/TIA	367 (34.1%)	72 (19.6%)	92 (40.9%)	94 (43.5%)	109 (34.1%)	0.089
Renal dysfunction	321 (33.2%)	46 (22.3%)	61 (27.1%)	80 (37.0%)	134 (41.9%)	< 0.001
Anemia	579 (59.9%)	91 (44.2%)	123 (54.7%)	134 (62.0%)	231 (72.2%)	< 0.001
Coronary artery disease	155 (16.0%)	34 (16.5%)	49 (21.8%)	25 (11.6%)	47 (14.7%)	0.027
Atrial fibrillation/flutter	314 (32.5%)	34 (16.5%)	67 (29.8%)	83 (38.4%)	130 (40.6%)	<0.001
Previous HF	407 (42.1%)	65 (31.6%)	130 (42.2%)	97 (44.9%)	150 (46.9%)	0.004
Clinical investigation						
SBP, mmHg	136 (117–157)	127 (113–149)	136 (118–161)	140 (120–157)	140 (116–158)	0.011
DBP, mmHg	74 (60–89)	80 (68–95)	76 (63–92)	73 (60–89)	67 (57–84)	< 0.001
HR, beats/min	92 (78–110)	97 (84–117)	92 (75–110)	94 (79–111)	88 (74–107)	< 0.001
Hemoglobin, g/dL	11.3 (9.7–13.0)	12.2 (10.6–14.0)	11.65 (10.03–13.40)	11.05 (9.40–12.80)	10.70 (9.30–12.10)	< 0.001
Serum creatinine, mmol/L	111.0 (85.0–160.0)	100.0 (75.5–137.0)	105.5 (85.0–146.3)	148.5 (105.0–186.3)	108.0 (82.0–155.0)	< 0.001
Serum sodium, mmol/L	136.8 (135.7–139.0)	136.7 (135.5–139.0)	136.5 (135.8–138.4)	137.0 (136.0–140.0)	137.0 (135.5–140.0)	0.202
Serum sodium ≤ 135 mmol/L	175 (18.1%)	25 (12.1%)	40 (17.8%)	42 (19.4%)	68 (21.2%)	0.061
LVEF ≤ 40%	425 (48.3%)	142 (68.9%)	105 (46.7%)	75 (34.7%)	103 (32.2%)	< 0.001
Outcomes during hospitalization						
Length of stay, days	9.0 (6.0–14.0)	9.0 (6.0–12.3)	8.0 (6.0–13.0)	9.5 (7.0–15.0)	10.0 (6.0–14.0)	0.014
In-hospital mortality	12.7%	5.3%	7.6%	14.8%	19.7	< 0.001

Data are presented as *n* (%) or median (IQR). ACS: acute coronary syndrome; DBP: diastolic blood pressure; HF: heart failure; HR: heart rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; SBP; systolic blood pressure; TIA: transient ischemic attack.

9–10 days showed no significant difference among the four age groups, the in-hospital mortality increased markedly with age, from 5.3% in the young patient group to 19.7% in the oldest-old patients ($P < 0.001$) (Table 1).

Survival analysis showed that short-term (30 days), mid-term (1 year), and long-term (3 years and 5 years) all-cause mortality post-discharge rose significantly with age (Figure 4A–4D). In unadjusted model for the prediction of death risk (Figure 4E–4H), death risk at 30 days in the middle-old group was approximately 1.4 times higher than in the young group (hazard ratio [HR] = 2.407, 95% confidence interval [CI]: 1.190–4.868, $P = 0.014$). In the old-old group,

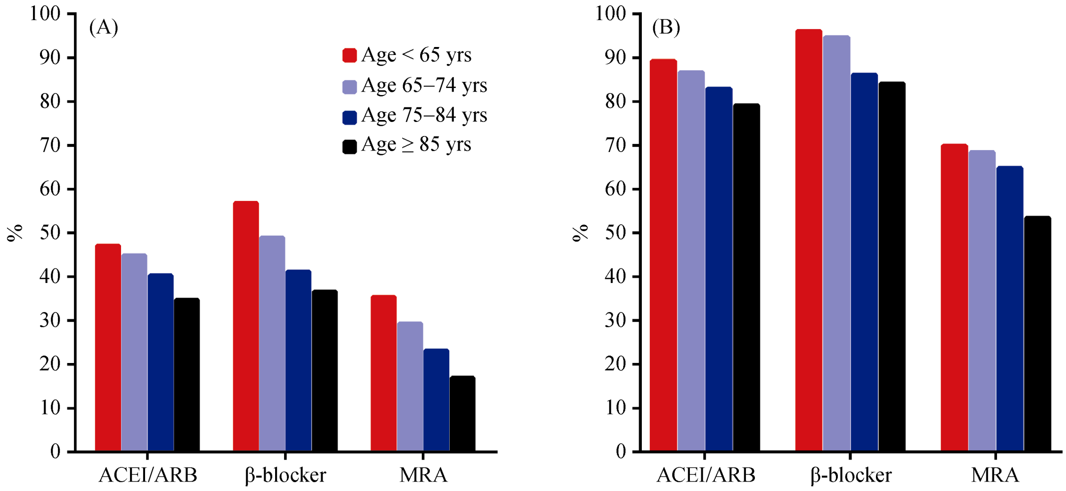

Figure 3. Evidence-based medication utilization at admission and discharge. (A): at admission; and (B) at discharge. ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist.

the mortality risk was approximately 2.4 times higher than in the young group (HR = 3.427, 95% CI: 1.719–6.833, P < 0.001), and the oldest-old group had 2.7 times higher risk than the young group (HR = 3.720, 95% CI: 1.865– 7.420, P < 0.001). Similar to the trends in short-term outcomes, the three old patient groups presented a higher risk of death compared with the young patient group at 1 year, 3 years, and 5 years.

3.7 Prognostic variables by age groups

Figure 5 showed that in a fully adjusted model for the prediction of death risk, medical history of HTN, DM, Af/AF, and clinical investigations including SBP, DBP, serum sodium levels, and hemoglobin at admission showed predictive value for short-, mid-, and long-term outcomes. However, the specific predictors varied significantly among the varying age groups in different time dimensions. But we still found some important common characteristics. For example, the sodium level at admission was consistently and significantly associated with the risk of death at 30 days in all the age groups. For the mid- and long-term outcomes, HTN and DM were independent risk factors in the young patient group. DBP showed the significant predictive value in the middle-old group. Af/AF, anemia, and hyponatremia markedly increase the risk of death in the old-old and oldest-old patient groups (Figure 5).

4 Discussion

To the best of our knowledge, this is the first cohort study on HF in Macao. We found that: (1) advanced age at the admission of HF patients in Macao was attributed to high-income level, aging population structure, and a well-established public health system. (2) The prevalence of HF increased significantly with age, and elderly patients (> 65 years) dominated the entire sample. Over half of the patients were over 75 years old and presented severe conditions and complicated comorbidities, which may cause significant health and economic burdens to society. (3) Marked heterogeneity existed in the epidemiological characteristics, clinical features, management, and outcomes among different age groups. (4) The utilization of evidence-based therapies was less frequent with increasing age. (5) The predictors of short-, mid-, and long-term mortality varied significantly among the different age groups, so age-based risk stratification models are urgently needed to understand the developing HHF trends in Chinese populations and guide research in aging societies.

Our study showed that the elderly HHF patients (≥ 65 years) had a markedly high prevalence (close to 80%) in Macao, especially the oldest-old (≥ 85 years), accounting for approximately one-third of the overall population. This distinctive demographic characteristic suggested that elderly HF patients have become a significant health and economic burden in Macao. The relatively high prevalence of the oldest-old patients in Macao may be treated as a consequence of multiple factors. First, due to the unique historical process, the residents in Macao have become acquainted with a novel way of life that merged Chinese traditional styles with Western modes since the mid of 16^{th} century. Macao became the epitome of a distinct hybrid culture and underwent urbanization several decades earlier than many other Asian countries and regions. Second, Macao is one of the most famous four casino cities in the world. The average income of Macao is leading most of the economies, even the developed countries like the US and Germany. High-income

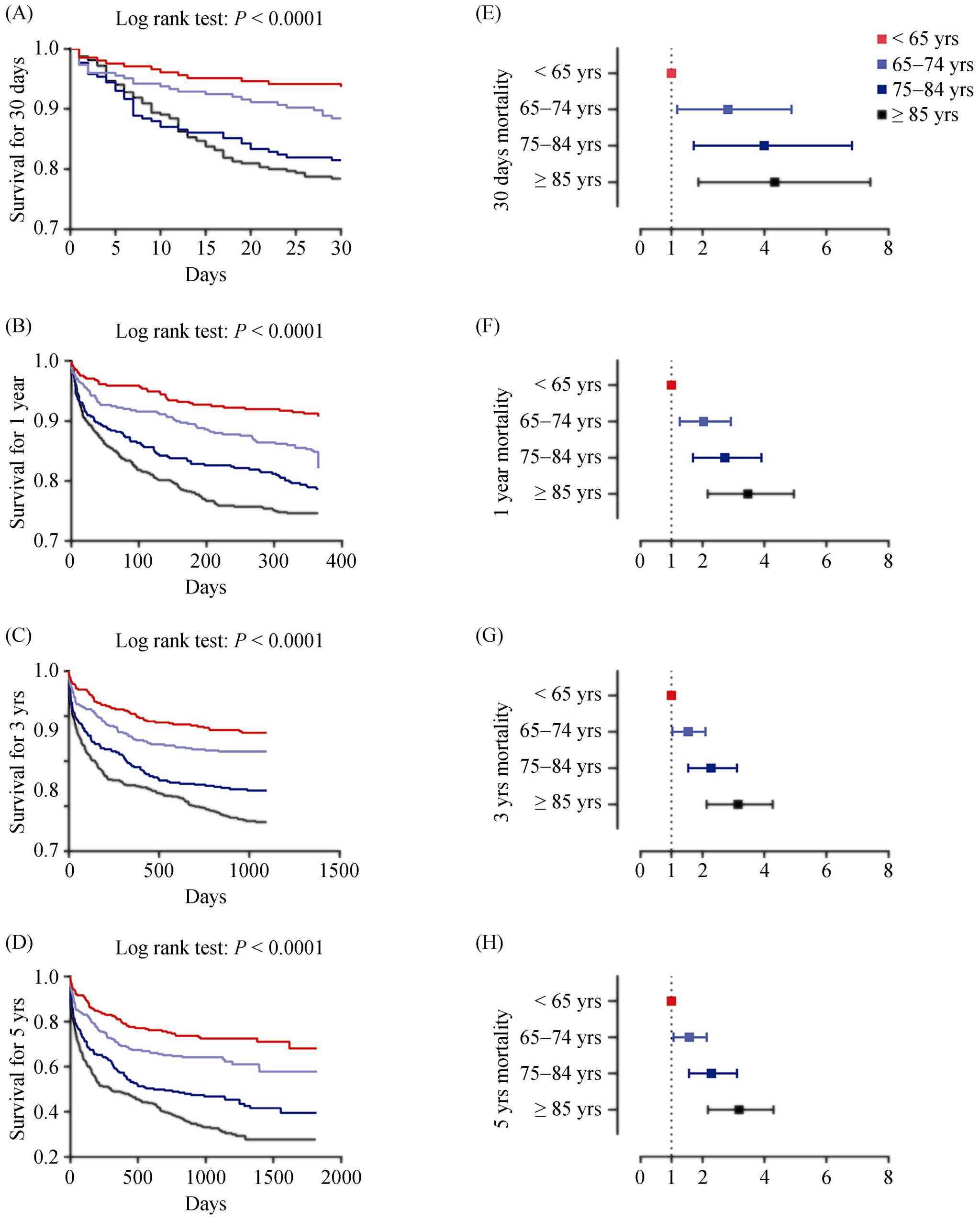

Figure 4. Kaplan-Meier survival curves and multivariate cox regression analyses for the prediction of risk of death according to the four age groups. (A–D): Kaplan-Meier survival curves by age groups for the patients hospitalized with acute heart failure in Macao; and (E–H): comparison of mortality rates according to the four age groups in our fully adjusted models.

level brings not only the improvement of living standards but also the modernization of the health care system and increasing aging population. In this study, we found economic development and population aging are significantly and positively related to admitted age of HF, confirming the previous finding that age at admission positively correlated with the human development index (a composite measure including life expectancy, adult literacy, educational level, and standard of living).[15] Third, although the degree of social aging in Macao was less severe than that in some developed countries such as the UK and Japan, the median admitted age of HF in Macao (82 years) was still 10 years older than in those regions (Japan 73.0 ± 14.0 years;[14] European countries 69.9 ± 12.5 years[8]). This interesting situation may be partly attributed to Macao's well-established public health system that especially cares for the elderly. On the one hand, seven health centers and three health stations in Macao provide free primary health care to all

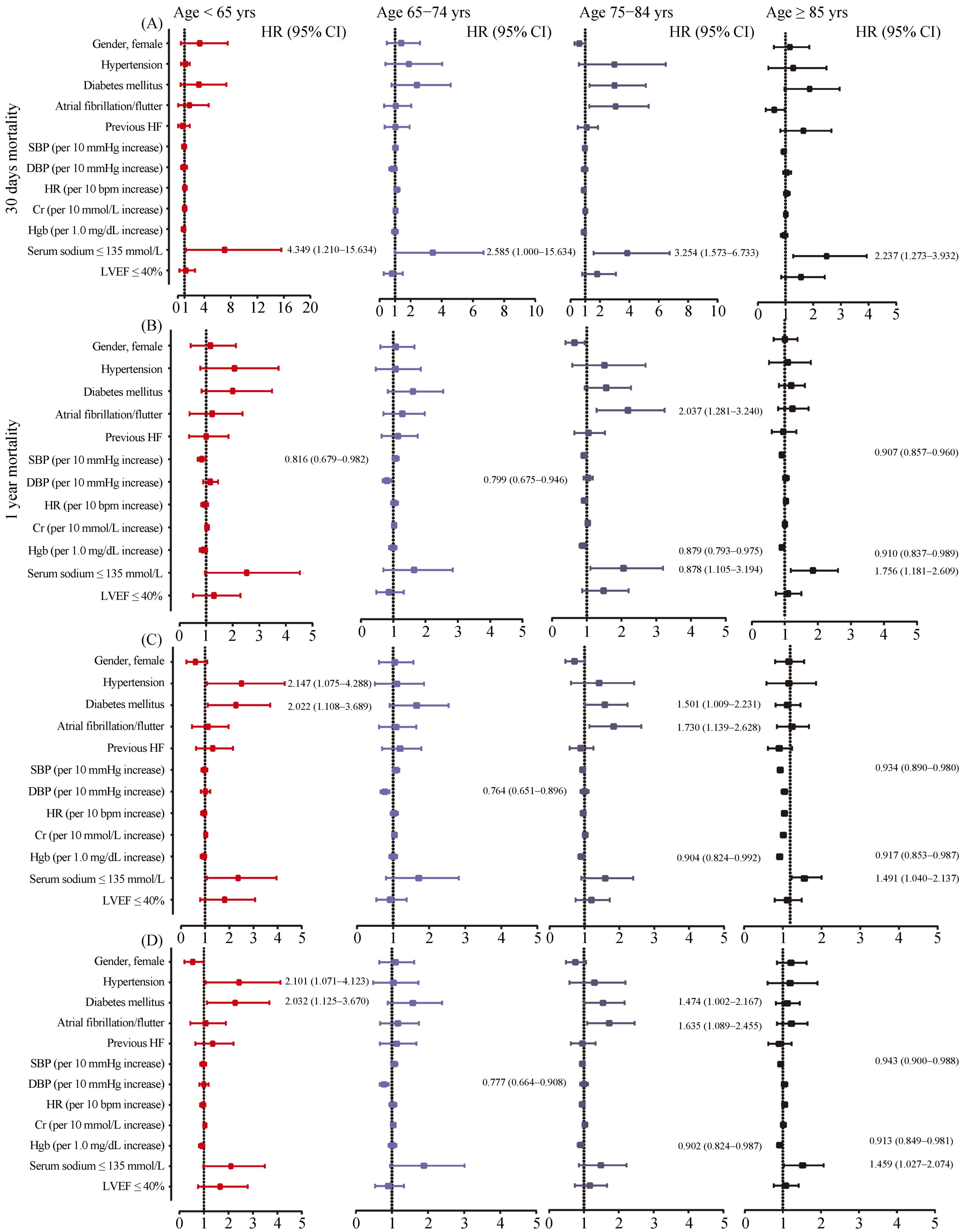

Figure 5. Adjusted hazard ratio (HR) forest plot of multivariate predictors of mortality in the four age groups at (A) 30 days, (B) 1 year, (C) 3 years, and (D) 5 years post-discharge. Cr: creatinine level; DBP: diastolic blood pressure; HF: heart failure; SBP: systolic blood pressure; Hgb: hemoglobin level.

residents, including chronic disease management, referrals to public hospitals, and special care for the disabled and the elderly. On the other hand, in Macao, medical service is 100% subsidized by the government for residents 65 years old and older, ensuring that they are fully cared for in primary care and during the hospitalization. These public health policies have played an essential role in increasing the average life expectancy and advanced admission age of HF patients in Macao.

We also found that more than 70% of the patients in the old-old and oldest-old groups required intensive care because of advanced age, severe conditions, and multiple cardiovascular comorbidities. Considering that the proportion of these two groups was approximately 50% of the overall HF population, we can infer that there is currently an unmet need in clinical and research endeavors regarding the intensive care of HF patients age ≥ 75 years in the future hospital-based registries.

Another meaningful finding in our research was that infection and HTN were more prone to induce ADHF in older patients, particularly in patients aged 75 years or older. These results indicated that, for the old-old and oldest-old groups, controlling blood pressure and preventing infection may play a crucial role in reducing the onset of ADHF.

Besides, the proportion of patients with non-compliance with therapy in Macao (4.9%) was much lower than that in Mainland China (8.4%)[18] and selected Western countries (13.1%).[5] Moreover, the prevalence of non-compliance with therapy was extremely low in the elderly HF patients (≥ 65 years) in Macao (only 3–4%), which could be partly explained by the reimbursement system that covers 100% payment for old patients (≥ 65 years) and 70% for adult patients younger than 65 years.

Despite the well-established health care system, the utilization of evidence-based therapies was less frequently with age. This finding is consistent with previous studies of elderly HF patients.[21] The causes of underprescription of evidence-based therapies in Macao may involve a variety of factors. For instance, general practitioners rather than cardiologists are in charge of HF patients in most health centers in Macao. Moreover, the higher prevalence of multiple comorbidities and polymerization in older patients may lead to premature cessation of treatment. In addition, the proportion of HF patients with preserved ejection fraction (HFpEF) increased markedly with age. For HFpEF, the therapies recommended by the guidelines are limited,[22] so underprescription of HF therapies may be more common in patients with this HF pattern. The use of evidence-based treatments significantly improved at discharge, which confirmed the evidence that reevaluation of current management and implementing evidence-based therapies by cardiologists are more frequent during hospitalization.[21,23,24] Therefore, there is an unmet need to establish multidisciplinary teams in health centers and hospitals to optimize the treatment of patients with HF in a controlled and monitored setting.

Finally, our study revealed that all-cause mortality during hospitalization and post-discharge increased significantly with age. Hyponatremia is strongly associated with 30-day all-cause death risk across all age groups, particularly in young patients. The pathogenesis of hyponatremia in HF is complex but closely related to severe renal dysfunction, excessive antidiuretic hormone secretion, and activation of the sympathetic and renin-angiotensin-aldosterone system at late stages of congestive HF.[25-28] As a result, this key indicator can be served as an independent predictor of short-term mortality in patients with HF. However, serum sodium levels at admission are not always consistent with long-term cardiac function post-discharge, so the predictive value of this indicator for long-term prognosis reduced. For mid- and long-term all-cause mortality, the different age groups had their specific prognostic predictors. Therefore, a reasonable approach is to develop specific risk stratification models and targeted interventions based on age groups to improve the long-term prognosis of HF patients.

4.1 Strengths and limitations

The five-year follow up of 98% was one of the important strengths of our study. In addition, the predictors of the short- and long-term prognosis of Chinese HF patients were fully analyzed for the first time in this study.

This study had several limitations. First, we had no information on the natriuretic peptide concentrations in the HF patients because the related testings have not been conducted at the public hospital in Macao until 2017. The primary diagnosis of HF in Macao was mainly based on the symptoms, signs, chest X-ray, and echocardiographic evaluation. Second, we did not collect information about the dosage of the specific HF treatment used in the subject studies. Third, cognitive dysfunction may have been present in elderly patients, especially in the oldest-old group, which has an important influence on the quality of life and outcomes in HF patients, but we did not assess the cognitive condition and quality of life in the study population.

4.2 Conclusion

There is currently an unmet critical need to assess the health and economic burden of HF in China's aging population. The present study, which used Macao as a model, demonstrated that the rapid economic development and a significant aging population had produced a profound impact on the epidemiological characteristics of HF in Chinese populations. Acute heart failure is predominantly a disease of the eldest in Macao, and significant heterogeneity existed in the clinical features, management, and outcomes among the different age groups. Age-based risk stratification models and multidisciplinary HF teams are urgently needed to improve the management and outcomes of HHF patients in Macao. These quality improvement initiatives and the experiences of Macao's well-established public health system may guide clinical and research endeavors in Chinese populations in the future.

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