Clinical Spectrum and Risk Factors for Heart Failure in Very Young Patients

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SOUHRN

Kontext: Prevalence srdečního selhání (HF) u mladších jedinců roste, což zpochybňuje tradiční vnímání HF jako onemocnění starších dospělých. Tento trend má významné klinické a ekonomické důsledky, protože HF vyžaduje celoživotní léčbu, což vede ke zvýšeným nákladům na zdravotní péči a ke snížené produktivitě.
Cíl: Cílem této studie je zkoumat klinické spektrum a základní rizikové faktory u pacientů s HF v mladém věku.
Metoda: Tato studie s kontrolní skupinou byla provedena na kardiologické klinice Hasna Medika Hospital v Cirebonu. Léčebnou skupinu tvořili pacienti s HF ve věku 17–40 let, kteří byli vyšetřeni v ambulanci nebo hospitalizováni v období od ledna 2023 do prosince 2023. Kontrolní skupinu tvořili pacienti bez srdečního selhání ve věku 17–40 let, kteří byli rovněž léčeni v ambulanci nebo hospitalizováni ve stejném období. Demografické údaje, rizikové faktory a komorbidity, jako je hypertenzní srdeční onemocnění (HHD), ischemická choroba srdeční (ICHS), diabetes mellitus 2. typu (DM2), fibrilace síní (FS) a chronické onemocnění ledvin (CKD), budou analyzovány jak bivariátně, tak multivariátně.
Výsledky: Celkem 190 vzorků ukazuje, že nejvyšší podíl tvoří ženy, přičemž 53,7 % žen jsou pacientky s HF a 55,8 % žen jsou pacientky bez HF. Podíl pacientů se srdečním selháním se zachovanou ejekční frakcí (HFpEF) je nejvyšší u pacientů s ICHS (35,42 %). ICHS a HHD jsou významně ($p < 0,001$) asociovány s HF ve velmi mladém věku s poměrem šancí (OR) 18,38 (95% interval spolehlivosti [CI] 6,86–49,29) a 4,39 (95% CI 2,19–8,83). Multivariační analýza v konečném modelu ukazuje, že ICHS a HHD jsou významně spojeny se srdečním selháním ve velmi mladém věku, s OR ICHS 15,57 (95% CI 5,72–42,34) a OR HHD 3,2 (95% CI 1,46–7,01).
Závěr: Srdeční selhání se může rozvinout v mladém věku, přičemž ICHS a HHD jsou významnými prediktory.

Keywords:
CAD
Heart failure
HHD
Young age

ABSTRACT

Background: The prevalence of heart failure (HF) in younger individuals is rising, challenging the traditional perception of HF as a disease of older adults. This trend carries significant clinical and economic implications, as HF requires lifelong management, leading to increased healthcare costs and reduced productivity.
Objective: This study aims to investigate the clinical spectrum and underlying risk factors of HF patients at young age.
Method: This case-control design study was conducted at HF Clinic of Hasna Medika Hospital in Cirebon. The case group were HF patients aged 17–40 years who were examined at outpatient clinic or admitted to hospital between January 2023 and December 2023. The control group were non-HF patients aged 17–40 years who were also treated at the outpatient clinic or admitted to hospital during the same period. Demographics data, risk factors, and comorbidities such as hypertension heart disease (HHD), coronary artery disease (CAD), type 2 diabetes mellitus (T2DM), atrial fibrillation (AF), and chronic kidney disease (CKD) will be analyzed both bivariate and multivariate.

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Results: A total of 190 sample shows that the highest proportion are female, with 53.7% female being HF patients and 55.8% female being non-HF patients. The proportion of patients with HFpEF is the highest in patients with CAD (35.42%). CAD and HHD are significantly (p <0.001) associated with HF at a very young age with an OR 18.38 (95% CI 6.86-49.29) and 4.39 (95% CI 2.19-8.83), respectively. Multivariate analysis in the final model shows that CAD and HHD are significantly associated with HF at a very young age, with an OR of CAD 15.57 (95% CI 5.72-42.34) and OR of HHD 3.2 (95% CI 1.46-7.01).
Conclusion: Heart failure can develop at a young age with CAD and HHD being a significant predictor.

Introduction

Heart failure (HF) is a clinical syndrome that affects all organs in the body. It is associated with high mortality and reduced quality of life.[1] The data from Heart Failure Society of America (HFSA) showed that the number of people with HF in America is expected to reach 8.5 million by 2030, with one in four people affected by HF. In Southeast Asia region, Indonesia ranks second in HF prevalence and has the highest 1-year crude mortality rate at 34% compare to other Asia country.[2,3] The data from HFSA also showed that HF occurs mostly in people over the age of 60, who are 20 times more likely to develop HF than people under the age of 60. However, studies conducted in Indonesia found that the average age of HF patients in Indonesia is 57 years old, which indicates younger HF patients.[2,4]

The prevalence of HF at a young age shows a significant increase, with an estimated 10% of HF patients under the age of 50. According to the French National Hospitalization Database, 4.7% of all HF patients are young (18–50 years). These young HF patients have a linear increase in traditional risk factors for ischemic heart disease such as hypertension, diabetes, smoking, obesity and dyslipidemia.[5,6] A study indicates that, in general, patients suffering from HF in Asia are younger than in Europe and America. However, they exhibit the highest prevalence of comorbidities, including renal dysfunction and diabetes. A more in-depth evaluation of the causative risk factors is needed.[7]

The development of HF at a young age is multifactorial, involving both cardiovascular and systemic contributors. Hypertension-induced cardiac remodelling, early-onset coronary artery disease (CAD), diabetes, atrial fibrillation (AF), and chronic kidney disease (CKD) would become a frequently found etiology in young patients with HF.[8]

The increase of HF incidence at a young age will lead to an increased economic burden of HF treatment, as HF treatment requires lifelong therapy.[9] Although the global economic burden of HF is not clearly known, the cost of HF therapy accounts for 2% of total healthcare costs in some countries and is increasing. For example, data in Korea shows that the cost of therapy for HF patients has increased by 50% in the last 5 years.[10]

Reduced quality of life and work productivity in young patients with HF is also a major concern.[11,12] This is because poor quality of life in HF patients is associated with a poor prognosis.[13] Based on some of the explanations above, assessing the risk of HF as early as possible will be very beneficial in reducing mortality, morbidity, economic burden and maintaining quality of life. This study aims to investigate the clinical spectrum and underlying risk factors of HF patients at young age.

Methods

Study design and participants

This study was conducted at the HF Clinic of Hasna Medika Hospital in Cirebon, utilizing a case-control design. Hasna Medika Cirebon Hospital was selected as the study site due to its role as a referral center for heart disease in the Cirebon city region. The case-control design was chosen based on the premise that heart failure (HF) cases in patients under 40 years of age are relatively uncommon, necessitating a comparative approach to identify potential risk factors.

The case group consisted of patients aged 17–40 years diagnosed with HF who were either examined at the outpatient clinic or admitted to the hospital between January 2023 and December 2023. To provide a robust comparison, the control group comprised patients aged 17–40 years who did not have a diagnosis of HF but were also treated at the outpatient clinic or admitted to the hospital within the same timeframe. This approach ensures that both groups share similar healthcare-seeking behaviors, minimizing potential selection bias.

To enhance the granularity of analysis, patients in both groups were stratified into three age subcategories: 17–24 years, 25–32 years, and 33–40 years, allowing for a more precise evaluation of age-related risk factors. To maintain the validity of comparisons and eliminate confounding factors, patients with congenital heart disease and rheumatic heart disease were excluded from both case and control groups. This exclusion criterion ensures that the study specifically investigates acquired causes of HF in younger individuals rather than conditions with a congenital or inflammatory etiology.

Data collection

The sample's medical records included demographics data, risk factors, and comorbidities such as hypertension heart disease (HHD), coronary artery disease (CAD), type 2 diabetes mellitus (T2DM), atrial fibrillation (AF), and chronic kidney disease (CKD). Other data collected were the results of echocardiograms that categorized patients according to ejection fraction (EF), those are patients with heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF).

Data analysis

Clinical characteristics of patients were presented in frequency and percentages. Bivariate analysis was assessed with Chi-square or Fisher exact test. Variables with p value <0.25 were included in a multivariate analysis model. Multivariate analysis was assessed using logistic regre-

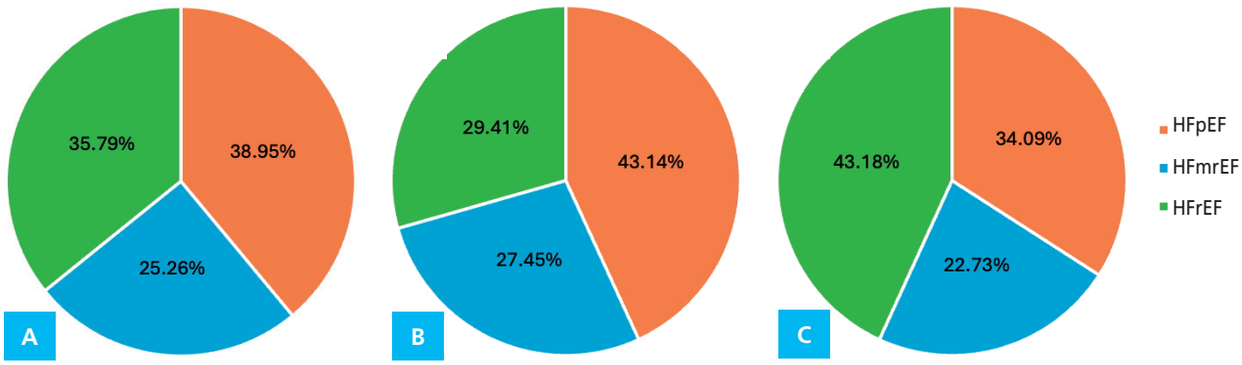

Fig. 1 – Heart failure categories based on ejection fraction. (A) In the overall sample aged 17–40 years, (B) in female aged 17–40 years, (C) in male aged 17–40 years
HFmrEF – heart failure with mildly reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction.

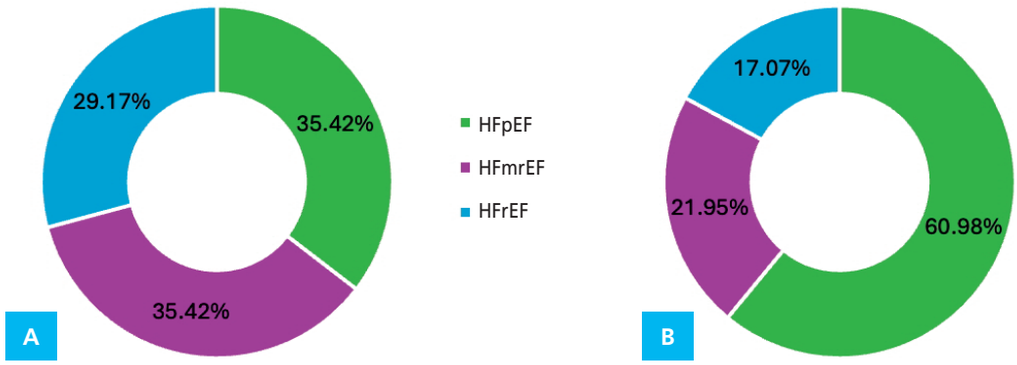

Fig. 2 – Heart failure categories in HF patients with (A) CAD and (B) HHD comorbidity.
HFmrEF – heart failure with mildly reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction

ssion through the backward method to obtain the final model. Data will also be sub-analyzed on the proportion of HF in the young population by EF, sex, CAD, HHD, and age group. The significance value in bivariate and multivariate analysis was p <0.05.

Results

A total of 190 sample shows that the highest proportion are female, with 53.7% female are HF patients and 55.8% female are non-HF patients. The age range of patients with HF is mostly 33–40 years (71.6%), with a mean age of 34.2 years. The majority of patients analyzed in this study lived in Cirebon and only a few patients who came from Majalengka. When comparing HF and non-HF patients, CAD (50.5% vs 5.3%), HHD (43.2% vs 14.7%), T2DM (10.5% vs 0%), AF (2.1% vs 0%) and CKD (6.3% vs 0%) are relatively more common in HF patients.

This study (**Figs 1A–1C**) find that the majority of HF patients aged 17–40 years has HFpEF (38.95%). Sub-analysis of the data shows that female patients have more HFpEF (43.14%) while male patients have more HFrEF (43.18%).

Figures 2A and 2B show that the proportion of patients with HFpEF is the highest in patients with CAD (35.42%).

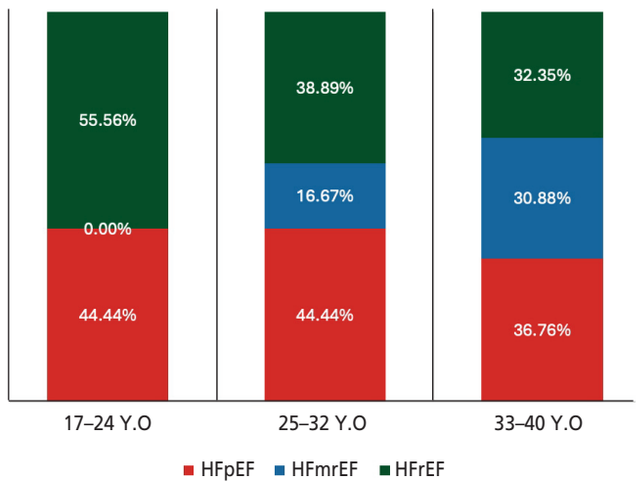

Fig. 3 – HF categories in patients aged 17–24 years, 25–32 years, and 33–40 years.

In contrast, the majority of patients with HHD has HFpEF, followed by HFmrEF and HFrEF at 60.98%, 21.95%, and 17.07% respectively. In the youngest age group (17–24 years), more than half of the patients has HFrEF (55.56%).

Table 1 – Bivariate analysis of variables

	p-value	OR	95% CI (lower–upper)
Male	0.771	1.09	0.62–1.93
Age group (years) 17–24 25–32 33–40	 0.009 0.340 0.007	 1 1.62 3.31	 0.60–4.33 1.39–7.84
CAD	<0.001	18.38	6.86–49.29
HHD	<0.001	4.39	2.19–8.83
T2DM	0.99	–	–
AF	0.568	2.02	0.18–22.68
CKD	0.99	–	–

AF – atrial fibrillation; CAD – coronary artery disease; CKD – chronic kidney disease; HHD – hypertensive heart disease; T2DM – type 2 diabetes mellitus.

Whereas in the age 25–32 years and 33–40 years, HFpEF is predominant (44.44% and 36.78%, respectively) (**Fig. 3**).

Based on bivariate analysis (**Table 1**), there is a higher proportion of HF in the 33–40 years age group compared to the 17–24 years age group (OR 3.31, 95%CI 1.39-7.84). The data also show that CAD and HHD are significantly (p <0.001) associated with HF at a very young age with an OR 18.38 (95% CI 6.86-49.29) and 4.39 (95% CI 2.19-8.83), respectively.

Multivariate analysis in the final model (**Table 2**) also shows that CAD and HHD are significantly associated with HF at a very young age, with an OR of CAD 15.57 (95% CI 5.72-42.34) and OR of HHD 3.2 (95% CI 1.46-7.01). The final model from the multivariate analysis had a predictive value of HF at young age (Y) = 19.317 (Constant) + 2.745 (CAD) + 1.163 (HHD).

Discussion

This study found a total of 95 HF patients at a young age (17–40 years) in a year. This number may be relatively small compared to the total number of HF patients. However, it is important to understand that these patients will undergo treatment for the rest of their lives and it will greatly affect their quality of life. These patients may also experience the risk of deterioration leading to death. A study at South Korea showed that the prevalence of HF based on gender at the age of 40 was similar, but it increases more in male than female at the age of 55. Then after 70 years old, it will be more in female than in male.[14] However, in this study, the proportion of young HF patients is higher in females than in males. These different data may be possible due to the prevalence of different risk factors in this study. These requires a deeper understanding by looking at several other risk factors.

Age-related pathways in HF

Systemic changes and cellular physiology will contribute to age-related alterations in the structure and function of the heart. Aging will increase the thickness of left ventricular wall and decrease in the regenerative capacity of heart muscle. Regeneration capacity is related to cardiomyocyte death and fibrosis in the heart muscle.[15] This study also found that the 35–40 age group suffered the most from HF (71.6%) compared to other younger age groups (17–24 and 25–32 years). Other studies that describe the proportion of HF at a young age are still very rare. The data from the MAGGIC study found that the proportion of HF patients <40 years old was 63%.[16] The systemic and heart structure changes that have occurred at a young age indicate the possibility of the cardiomyocyte damage occurring much earlier. The data from this study also show that a decrease in EF <40% has already occurred in the majority of patients aged 17–24 years (55.56%). The proportion of HFrEF cases in other age groups is not low either. Although studies show no significant difference in mortality in HFrEF, HFmrEF, or HFpEF.[17]

Aging is undoubtedly an independent risk factor for HF. Even without overt injury, structural and functional changes to the heart will still occur with aging. Normal aging generally appears to be a thickening and stiffening of the left ventricular wall, especially the septum, dilatation of the left atrium, and increased fibrosis of the heart muscle.[18] However, in the HF cases at a very young age as in this study, other risk factors must have a major effect in causing damage to the heart structure. Traditional risk factors for ischemic heart disease need to be considered.[13]

Coronary artery disease and hypertension: a deadly combination

Any CAD that occurs before the age of 55 years in male or 65 years in female is called 'premature' CAD. Premature CAD is associated with poor long-term outcomes, with

Table 2 – Multivariate analysis of variables

	Full model			Final model		
	Coefficient b	*p*-value	OR (95% CI)	Coefficient b	*p*-value	OR (95%CI)
Age group (years) 17–24 25–32 33–40	 0.322 0.45	 0.659 0.557 0.362	 1 1.38 (0.47–4.05) 1.57 (0.6–4.13)	 –	 –	 –
CAD	2.66	<0.001	14.32 (5.17–39.67)	2.745	<0.001	15.57 (5.72–42.34)
HHD	1.13	0.005	3.1 (1.41–6.81)	1.163	0.004	3.2 (1.46–7.01)
Constant	-1.24			19.317		

CAD – coronary artery disease; HHD – hypertensive heart disease.

Table 3 – Baseline characteristics of study sample

Variables	Total (n = 190)	HF patients (n = 95)	Non-HF patients (n = 95)
Gender			
Female	104 (54.7)	51 (53.7)	53 (55.8)
Male	86 (45.3)	44 (46.3)	42 (44.2)
Age group (years)			
17–24	30 (15.8)	9 (9.5)	21 (22.1)
25–32	44 (23.2)	18 (18.9)	26 (27.4)
33–40	116 (61.1)	68 (71.6)	48 (50.5)
Mean ± SD	32.41±6.36	34.23±5.58	30.59±6.59
Residence			
Cirebon	146 (76.8)	70 (73.7)	76 (80)
Kunngan	11 (5.8)	7 (7.4)	4 (4.2)
Indramayu	11 (5.8)	9 (9.5)	2 (2.1)
Majalengka	7 (3.7)	2 (2.1)	5 (5.3)
Others	15 (7.9)	7 (7.4)	8 (8.4)
CAD			
No	137 (72.1)	47 (49.5)	90 (94.7)
Yes	53 (27.9)	48 (50.5)	5 (5.3)
HHD			
No	135 (71.1)	54 (56.8)	81 (85.3)
Yes	55 (28.9)	41 (43.2)	14 (14.7)
T2DM			
No	180 (94.7)	85 (89.5)	95 (100)
Yes	10 (5.3)	10 (10.5)	0
AF			
No	187 (98.4)	93 (97.9)	94 (98.9)
Yes	3 (1.6)	2 (2.1)	1 (1.1)
CKD			
No	184 (96.8)	89 (93.7)	95 (100)
Yes	6 (3.2)	6 (6.3)	0

AF – atrial fibrillation; CAD – coronary artery disease; CKD – chronic kidney disease; HF – heart failure; HHD – hypertensive heart disease; T2DM – type 2 diabetes mellitus.

an estimated 4–10% experiencing an acute myocardial infarction. Understanding the process of premature CAD is very important to prevent the increasing prevalence of CAD at a young age.[19,20]

Based on the baseline characteristics in this study (**Table 1**), the proportion of CAD in HF patients was 50.5% compared to 5.3% in non-HF patients. This shows that half of HF patients have CAD at a young age, which can be called premature CAD. The cause of CAD at a young age is thought to be multifactorial based on several studies. An observational study has found that ethnicity, inflammatory diseases and behavioral risk factors are associated with the occurrence of premature CAD. Identifying healthy young populations at risk of early-onset CAD is challenging due to the limited number of studies quantifying risk factors and the limited sensitivity of existing screening modalities. Similarly, in terms of prevention in young people at risk of CAD, statin recommendations have not been made in the under-40 age group due to limited trials.[20–22]

Studies show that the most common cardiovascular risk factors for CAD are smoking, dyslipidemia, and family history of premature CAD. These three conventional risk factors are early signs of CAD. Smoking behavior can be intervened with education to quit smoking, as well as dyslipidemia can be intervened with good dietary changes. However, a family history of premature CAD requires confirmation of genetic analysis which not all health services can perform.[23,24]

Globally, hypertension ranks third among the major risk factors for cardiovascular disease. Data from the Indonesian Health Survey in 2023 showed that the prevalence of hypertension in the age group of 18–24 years was 10.7% and 17.4% in the age of 25–34 years. Hypertension is often referred to as the 'silent killer' because complications can occur without obvious symptoms.[25,26]

This study revealed that almost half of the patients diagnosed with heart failure (43.2%) had hypertension, in comparison to only 14.7% of patients diagnosed with non-heart failure who had hypertension (**Table 3**). The Hypertension Society recommends that hypertensive patients under the age of 40 should be referred to a hypertension specialist to exclude secondary hypertension and determine the optimal therapeutic regimen. It is important to note that young patients who experience hypertension-mediated organ damage (HMOD) are at risk of death from cardiovascular disease, as this condition will not fully reverse.[27,28]

Hypertensive heart disease (HHD) is currently the second most common cause of HF. HHD has been associated with left ventricular morphological changes and abnormalities in left ventricular function, with signs of left ventricular hypertrophy. The co-occurrence of HHD and CAD is particularly deleterious, especially in younger age. The present study utilizes both bivariate and multivariate analyses to demonstrate an unequivocal association between CAD and HHD with HF in young age.[29,30] This study found that CAD increased the risk of HF at a young age by 15 times, while HHD increased the risk by 3 times. Consequently, it can be deduced that patients who have been diagnosed with CAD, HHD, or both at a young age are likely to face a significantly higher risk of developing HF.

The younger the age the worse the prognosis

Heart failure at a very young age is not common, but when it does occur, the prognosis and health burden are worse. Even in younger patients, especially those <40 years of age, cardiovascular events remain frequent, with mortality rates reaching more than 10% within one year.[31] Studies showed that the likelihood of reduced life expectancy is very high for HF diagnosed between the ages of 20 and 36. By the age of 20, the estimated loss of life expectancy reaches 36 years in 50% of HF patients.[12,32] Based on a global meta-analysis study of chronic heart failure (MAGGIC), young people with HF have different clinical characteristics, including different etiologies, more severe left ventricular dysfunction, but less severe symptoms. The more severe the left ventricular function, the greater the likelihood of fibrosis of the heart muscle. This puts the patient at a greater risk of fatal arrhythmias leading to death.[16,33] Current recommendations for HF therapy, particularly in HFrEF, are optimal for reducing the risk of death in HF patients. However, specific data on very young patients are still lacking.[16]

Limitation and future research

This study has some limitations that must be considered. First, this study was only conducted in one hospital, a cardiovascular center hospital, therefore the population involved as a research sample may not represent the data in a larger population. Second, there are no data on behaviors such as smoking, exercise, diet, which may also influence the presence of CAD or HHD as a major risk factor. Third, the laboratory data were incomplete, so it could not be analyzed thoroughly. Fourth, this study did not include details of the HF subset that occurred in the patients, so the possibility of cardiomyopathy or myocarditis as one of the variables could not be excluded. Future studies that are more thorough and detailed are needed to understand the risk factors for someone who develops HF at a very young age.

Conclusions

Heart failure is plausible in young age with a clinical spectrum predominantly of preserved ejection fraction. Early CAD and HHD are important predictors of heart failure at a young age. Effective risk factor prevention and screening strategies are imperative for high-risk young age groups.

Credit authorship contribution statement

YP and FH contributed to data collection and data editing. YP and WP compiled and analyzed statistical data. The research study design, methods, sample size were discussed and compiled by YP and HH. The study results, analyses, and discussions were elaborated and evaluated by YP, BB, and NA. Manuscript preparation and journal submission process were conducted by YP and WP.

Conflict of interests

There are no conflicts of interest in this study.

Ethical statement

This study has received ethical approval from the ethics commission of Gunung Jati Hospital Cirebon.

Informed consent

This study did not take informed consent because it was based on secondary and retrospective data.

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