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Impact of female sex and type 2 diabetes mellitus on in-hospital mortality among patients with acute coronary syndrome: a retrospective cohort study between 2015-2022

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Aim. This study aimed to assess the influence of female sex and type 2 diabetes mellitus (T2DM) on in-hospital mortality among patients diagnosed with acute coronary syndrome (ACS) in the emergency department during the period 2015-2022, while also exploring the association of relevant laboratory factors.
Material and methods. An observational, analytical, retrospective cohort study was conducted, focusing on patients diagnosed with acute coronary syndrome who had high-density lipoprotein (HDL) values measured. The study included a total of 196 patients, divided into diabetes and non-diabetes groups, totaling 98 patients in each.
Results. Among the 196 patients with acute coronary syndrome, 181 survived, and 15 succumbed until hospital discharge. Statistically significant associations were identified between female sex (relative risk (RR): 3.52, 95% confidential interval (CI): 1.25-9.92, p=0.017) and T2DM (RR: 4.05, 95% CI: 1.51-10.85, p=0.005) with an increased risk of mortality in acute coronary syndrome patients. Notably, high HDL values did not exhibit a statistically significant association (RR: 0.88, 95% CI: 0.33-2.33, p=0.789). Subsequent multivariate analysis reaffirmed the significant association, indicating a 20% increased risk of death in patients with T2DM and acute coronary syndrome (RR: 1.2, 95% CI: 0.15-2.25, p=0.025).
Conclusion. The study concludes that while elevated HDL levels are not associated with increased in-hospital mortality in acute coronary syndrome patients, T2DM emerges as a noteworthy factor influencing this outcome.

Keywords: high-density lipoprotein cholesterol, acute coronary syndrome, in-hospital mortality, risk factors, observational study.

Relationships and Activities: none.

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ACS — acute coronary syndrome, ASCVD — atherosclerotic cardiovascular disease, CI — confidential interval, CKD — chronic kidney disease, HDL — high-density lipoprotein, NSTE-ACS — non-ST-elevation acute coronary syndrome, RR — relative risk, STE-ACS — ST-elevation acute coronary syndrome, T2DM — type 2 diabetes mellitus

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Влияние женского пола и сахарного диабета 2 типа на госпитальную смертность пациентов с острым коронарным синдромом: ретроспективное когортное исследование в период 2015-2022

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Цель. Оценить влияние женского пола и сахарного диабета (СД) 2 типа на госпитальную смертность среди пациентов с острым коронарным синдромом (ОКС) в отделениях неотложной помощи в период 2015-2022, а также изучить связь соответствующих лабораторных факторов.
Материал и методы. Было проведено наблюдательное, аналитическое, ретроспективное когортное исследование, в котором основное внимание уделялось пациентам с острым коронарным синдромом, у которых измерялся уровень липопротеинов высокой плотности (ЛВП). В исследование были включены в общей сложности 196 пациентов, разделенных на 2 группы по 98 пациентов с наличием и отсутствием СД 2 типа.
Результаты. Из 196 пациентов с острым коронарным синдромом 181 выжил, а 15 скончались до выписки из стационара. Статистически значимые связи были выявлены между женским полом (относительный риск (RR): 3,52, 95% доверительный интервал (ДИ): 1,25-9,92, p=0,017) и СД 2 типа (RR: 4,05, 95% ДИ: 1,51-10,85, p=0,005) и повышенным риском летального исхода у пациентов с ОКС. Примечательно, что высокие значения ЛВП не имели статистической значимости (RR: 0,88, 95% ДИ: 0,33-2,33, p=0,789). Последующий многомерный анализ подтвердил 20% увеличение риска летального исхода у пациентов с СД 2 типа и ОКС (RR: 1,2, 95% ДИ: 0,15-2,25, p=0,025).
Заключение. Исследование показало, что, хотя повышенные уровни ЛВП не связаны с увеличением госпитальной смертности у пациентов с ОКС, СД 2 типа заслуживает внимание как фактор, оказывающий статистически значимое влияние на смертность.

Ключевые слова: липопротеины высокой плотности, острый коронарный синдром, госпитальная смертность, факторы риска, наблюдательное исследование.

Отношения и деятельность: нет.

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According to the World Health Organization, cardiovascular diseases are the leading cause of death in Latin America, and demographic and lifestyle changes associated with epidemiological changes are causing large-scale epidemics [1, 2].

Acute coronary syndrome (ACS) is a life-threatening manifestation of atherosclerosis. It is usually caused by acute thrombosis due to rupture or erosion of a coronary atherosclerotic plaque, with or without vasoconstriction, resulting in a sudden and severe reduction in coronary blood flow [3, 4].

Epidemiological data consistently show that non-ST-elevation coronary syndromes (NSTE-ACS) occur more frequently than ST-elevation acute coronary syndromes (STE-ACS). The annual incidence is approximately 3 per 1,000 inhabitants, but varies depending on the country [3, 4]. In-hospital mortality was higher in patients with NSTE-ACS than in those with NSTE-ACS (7% vs. 3-5%), but was similar at 6 months (12% vs. 13%) [5, 6].

High-density lipoprotein (HDL) prevents atherosclerosis by removing excess cholesterol from macrophages through pathways involved in reverse cholesterol transport [6, 7]. HDL also inhibits lipid oxidation, restores endothelial function, exerts anti-inflammatory and antiapoptotic effects, and has also been shown to exert anti-inflammatory effects in animal models [4, 6]. Such properties may contribute significantly to HDL's ability to suppress atherosclerosis.

It has been suggested that systemic and vascular inflammation alters HDL to a dysfunctional form, altering its antiatherogenic effects [7, 8]. Another significant factor in HDL dysfunction may be a loss of anti-inflammatory and antioxidant proteins, possibly along with a gain of pro-inflammatory proteins [7, 9]. Myeloperoxidase, a proinflammatory enzyme, causes specific residues in plasma and arterial apolipoprotein AI to undergo oxidative modification and nitrosylation, rendering HDL dysfunctional. This affects ABCA1 macrophage transport, activates inflammatory pathways, and increases the risk of coronary artery disease [8, 10]. Low plasma HDL cholesterol is a strong and independent risk factor for atherosclerotic cardiovascular disease (ASCVD). However, several large studies recently revealed that pharmacological interventions that increase HDL concentration have not improved cardiovascular outcomes when added to standard therapy [10, 11]. Furthermore, specific genetic variants that raise HDL levels are not clearly associated with a reduced risk of coronary heart disease [12, 13]. These observations have challenged the hypothesis that HDL is causally related to ASCVD and that intervention to raise HDL will reduce ASCVD events [13, 14].

There is compelling data that the ability of HDL to promote cholesterol efflux from macrophages, the first step in the "reverse cholesterol transport" pathway, is inversely associated with ASCVD risk even after controlling for HDL [14, 15]. This has led to the HDL flux hypothesis that therapeutic intervention targets cholesterol efflux from macrophages and may reduce risk [16]. Preclinical studies of such interventions are promising and early phase clinical studies, although small, are encouraging. However, new findings and therapies targeting HDL are promising and may provide an important intervention on the burden of ASCVD in the future [16, 17].

Recent studies have evaluated cardiovascular outcome and mortality in patients treated with HDL-modulating medications [17, 18]. Clinical trials of niacin, fibrates, and CETP inhibitors included a total of 117,411 patients and found no decrease in all-cause mortality, coronary heart disease, myocardial infarction, or stroke [18, 19]. Likewise, other trials of niacin or CETP inhibitors involving 69,515 patients did not find a decrease in overall cardiovascular mortality [20, 21].

In addition to disappointing randomized clinical trials of HDL-raising drugs, human genetics studies have failed to support the conventional HDL hypothesis. Genetic variants are inherited randomly and can be seen as a natural form of randomized clinical trial, a process known as "Mendelian randomization". There has been substantial interest in the question of whether genetic variants that raise HDL reduce the risk of ASCVD or, conversely, those that lower HDL increase the risk of ASCVD. This not only casts doubt on the specific approach of inhibiting endothelial lipase to reduce the risk of ASCVD, but also casts additional doubt on the HDL hypothesis[1] [22].

Mazidi M, et al. (Poland, 2018) prospectively investigated the association between extremely low and high HDL-C with the overall risk of coronary heart disease, cerebrovascular disease, and cancer mortality. The analysis was based on subjects ⩾18 years of age from the National Health and Nutrition Examination Surveys (NHANES). They classified HDL-C levels as: ⩽30: extremely low, 30-40: low, 40-80: reference, 80-100: high, and ⩾100: extremely high. After adjustment, they found that very low HDL-C had three times the risk of total mortality. The RR for mortality from CHD and stroke was 2.00 and 2.53, respectively; Likewise, subjects with extremely high levels of HDL-C had a higher risk of mortality ($p<0.001$).

[1] Rivera J. Relación entre alteración de niveles de colesterol HDL-C y colesterol NO HDL-C en infarto agudo de miocardio en adultos hospitalizados en el Hospital José Carrasco Arteaga, período enero-diciembre 2018 [Internet]. Cuenca: Universidad Católica de Cuenca; 2020 [citado el DIA de MES de AÑO]. Disponible en: https://dspace.ucacue.edu.ec/handle/ucacue/8358.

Table 1

Clinical characteristics of patients with acute coronary syndrome according to mortality

	Mortality		RR [95% CI]	p value
	Survivors, n=181 (%)	Deceased, n=15 (%)		
Age (years)[a]	68 (16)	72 (8)	1.04 [1.00-1.07]	0.050
Sex			3.52 [1.25-9.92]	0.017
Female	61 (33.7%)	10 (66.7%)		
Male	120 (66.3%)	5 (33.3%)		
Arterial hypertension			0.88 [0.33-2.32]	0.789
Yes	103 (56.9%)	8 (53.3%)		
No	78 (43.1%)	7 (46.7%)		
Type 2 Diabetes mellitus			4.05 [1.51-10.85]	0.005
Yes	44 (24.3%)	9 (60.0%)		
No	137 (75.7%)	6 (40.0%)		
Chronic Kidney Disease			2.38 [0.87-6.54]	0.092
Yes	29 (16.0%)	5 (33.3%)		
No	152 (84.0%)	10 (66.7%)		
Obesity			1.94 [0.66-5.7]	0.231
Yes	27 (14.9%)	4 (26.7%)		
No	154 (85.1%)	11 (73.3%)		
Hypercholesterolemia			1.19 [0.42-3.34]	0.741
Yes	53 (29.3%)	5 (33.3%)		
No	128 (70.7%)	10 (66.7%)		
Hypertriglyceridemia			0.9 [0.27-3.03]	0.865
Yes	148 (81.8%)	12 (80.0%)		
No	33 (18.2%)	3 (20.0%)		
HDL			0.88 [0.33-2.33]	0.789
High	91 (50.3%)	7 (46.7%)		
Normal	90 (49.7%)	8 (53.3%)		

Note: Bivariate Poisson regression model with robust variance; Statistically significant level: p<0.05; Descriptive Statistics: Median (Interquartile Range): [a] — Median (IQR).

Abbreviations: CI — confidential interval, HDL — high-density lipoprotein, RR — relative risk.

Therefore, they conclude that extremely low and high levels of HDL-C were associated with a higher risk of mortality (total, coronary heart disease, and stroke) [23].

Madsen C, et al. (Denmark, 2017) included a total of 52,268 men and 64,240 women from two prospective population-based studies. During 745,452 person-years of follow-up, the number of deaths from any cause was 5619 (mortality rate, 17.1/1000 person-years 95% confidential interval (CI): 16.7-17.6) in men and 5059 (mortality rate, mortality, 12.1/1000 person-years (11.8-12.4)) in women. The association between HDL cholesterol concentrations and all-cause mortality was U-shaped for both men and women, with both extremely high and low concentrations being associated with a high risk of all-cause mortality. The HDL cholesterol concentration associated with the lowest all-cause mortality was 1.9 mmol/L (95% CI: 1.4-2.0) (73 mg/dL (54-77)) in men and 2.4 mmol/L (1.8-2.5) (93 mg/dL (69-97)) in women [17].

Hamer M, et al. (Australia, 2018) recruited 37,059 adults (age =57.7±11.9 years; 46.8% men) from household surveys of the general population and linked to the British National Health Service Central Register to record mortality. There were 2,250 deaths from all causes during 326,016 person-years of follow-up. When compared with the reference category (HDL-C =1.5-1.99 mmol/L), a U-shaped association was observed for all-cause mortality, with an elevated risk in participants with the lowest (hazard ratio =1.23; 95% CI: 1.06-1.44) and the highest concentration (1.25, 0.97-1.62) of HDL-C [24].

Despite incontrovertible epidemiological evidence of the inverse association of HDL with ASCVD risk, the available data in humans are not consistent with this causal relationship and therefore do not support the conventional HDL hypothesis. However, recent studies have focused on the function of HDL and suggest a possible approach to reconcile human and animal data and point to a potential avenue to target HDL therapeutically. Therefore, better clinical understanding of the traits of dysfunctional HDL or apolipoprotein AI may lead to new diagnostic and treatment modalities for ACS.

Material and methods

Study design: an observational, analytical and retrospective cohort study was designed.

Study population: the target population was composed of patients admitted to the emergency service with a primary diagnosis of ACS during the period from January 2015 to December 2022. The exposed group included those patients of both sexes aged 18 years or older who presented HDL levels greater than 60.0 mg/dl in the initial evaluation in the

Table 2

Multivariate analysis of associated factors and mortality

	Mortality, RR [95% CI]	p value
Age (years)[a]	0.02 [-0.03 — -0.07]	0.394
Sex		
Female Male	1.05 [-0.04 — -2.13]	0.058
Diabetes mellitus type 2		0.025
Yes	1.2 [0.15 — 2.25]	
No	Ref.	

Note: Bivariate Poisson regression model with robust variance; Statistically significant level: p<0.05; Descriptive Statistics: Median (Interquartile Range): [a] — Median (IQR).

Abbreviations: CI — confidential interval, RR — relative risk.

emergency room. On the contrary, the unexposed group consists of patients with HDL levels that ranged between 40 and 60 mg/dl. Strict exclusion criteria encompass people with a history of coronary heart disease, those with a familial predisposition to coronary heart disease, and those with incomplete data.

Definitions of the variables included. We considered the following parameters in the evaluation of the variables included in the study. Hypertension (systolic blood pressure >130 mmHg and diastolic blood pressure >80 mmHg), type 2 diabetes mellitus (T2DM) (fasting glucose >126 mg/dL and postprandial glucose >200 mg/dL), presence or absence of kidney damage for chronic kidney disease (CKD), a body mass index >30 kg/m^2 for obesity, total cholesterol levels >200 mg/dL for hypercholesterolemia, triglyceride levels >150 mg/dL for hypertriglyceridemia, and high levels of HDL cholesterol (HDL >60 mg/dL) (Table 1).

Data collection and processing. Rigorous data collection procedures were implemented, using a structured approach to extract relevant information from patient records. Microsoft Excel 2021 and SPSS statistical software facilitated comprehensive data processing. Descriptive statistics involved the creation of intricate one- and two-dimensional frequency tables, which offered nuanced information about absolute and relative values. The tables were accompanied by graphical representations to improve the visualization of the data.

Statistical analysis. The analytical phase employed a wide range of statistical tests adapted to the nature (qualitative or quantitative) and distribution of the variables. To evaluate whether elevated HDL levels serve as a discernible risk factor for ACS-related mortality, the chi-square test was meticulously applied for qualitative variables, with a predetermined significance level of 5%. Furthermore, the association between elevated HDL levels and the risk of death from ACS was explored by calculating relative risks and corresponding 95% confidence intervals. Given the predominantly qualitative nature of the intervening variables, their potential impact on ACS mortality was rigorously analyzed using the chi-square test, selectively excluding quantitative variables.

Ethical considerations. Ethical approval for the protocol was diligently sought and obtained from both the institutional ethics committee and the hospital. The study protocol scrupulously adheres to the principles of confidentiality in information management, aligning with the ethical guidelines established in the Declaration of Helsinki and the recommendations of the Council of International Organizations of Medical Sciences (CIOMS) for biomedical research. This ensures maximum integrity and ethical conduct throughout the research process.

Results

Of the 196 patients admitted to the emergency department, 98 were selected for the exposed cohort group and another 98 for the non-exposed cohort group. The clinical characteristics of patients with acute coronary syndrome according to mortality are presented below. It is observed that the median age of the survivors was 68 years, compared to 72 years in the deceased (RR: 1.04, 95% CI: 1.00-1.07, p=0.050). Regarding gender, 33.7% of women died, while 66.7% of men died (RR: 3.52, 95% CI: 1.25-9.92, p=0.017) (Table 1).

In relation to comorbidities, the presence of T2DM showed a significant association with mortality (RR: 4.05, 95% CI: 1.51-10.85, p=0.005). No significant associations with mortality were found for high blood pressure, CKD, obesity, hypercholesterolemia, hypertriglyceridemia, and HDL levels.

Subsequently, a bivariate analysis of each variable in comparison with mortality was carried out, using a Poisson regression model with robust variance. The latter confirmed the statistical significance of these results (p<0.05) (Table 2).

Discussion

In this study, it was evident that the average age of the surviving patients was 68 years, in contrast to the deceased patients, whose average age was 72 years. The current research found a statistically significant association, indicating that increasing age increases the risk of dying by 4% in patients with ACS (RR: 1.04, 95% CI: 1.00-1.07, p=0.050). This association supports previous findings suggesting that ACS in older adults presents relatively worse outcomes due to high atherosclerotic plaque burden, anatomical complexity, and the presence of various age-related comorbidities, thus contributing to a worse prognosis [25, 26].

In relation to gender, it was observed that 66.3% of the deceased were women and 33.3% were men, evidencing a statistically significant association between sex and mortality in patients with ACS. However, the multivariate analysis did not show a direct association between being female and in-hospital mortality in patients with SICA. Other studies have reported that men are more likely

to suffer from AHF, but our observations revealed that women had a higher prevalence of angina due to risk factors such as diabetes, hypertension, hypercholesterolemia and obesity, which increases cardiovascular risk and in-hospital mortality in women more than in men [27, 28].

Among the comorbidities evaluated, arterial hypertension did not show significant association with in-hospital mortality in patients with ACS. Although hypertension is a well-established cardiovascular risk factor, its relationship with mortality varies in different studies. Another study reported that hypertension is associated with increased in-hospital and 6-month mortality, especially in cases with elevated blood pressure levels [29, 30].

Regarding T2DM, a statistically significant association was found with in-hospital mortality in patients with ACS. The multivariate analysis confirmed this association, indicating that the presence of T2DM increases the risk of death in patients with ACS by 20%. Numerous studies support the idea that diabetes mellitus is a marker of poor prognosis in patients with ACS, increasing the risks of ischemic and hemorrhagic complications [31, 32].

Regarding CKD, no statistically significant association with in-hospital mortality was found in our study. However, previous studies have indicated that patients with CKD have worse outcomes compared to those without kidney disease, due to a lower likelihood of receiving standard treatment and reperfusion. CKD is associated with a significant increase in short- and long-term mortality in patients with ACS [33-35].

Obesity did not demonstrate significant association with in-hospital mortality in patients with ACS in our study. These findings are consistent with previous studies suggesting that mortality risk does not follow linear pattern with body weight, and results may vary depending on the population studied [36, 37].

Regarding the lipid profile, neither hypercholesterolemia nor hypertriglyceridemia was significantly associated with in-hospital mortality in our study population. These results differ from previous research that has suggested a relationship between extremely high triglyceride levels and an increased risk of mortality in patients with ACS [38].

Finally, in relation to HDL levels, no statistically significant association was found with in-hospital mortality in patients with ACS in our study. Conversely, some studies have suggested that extremely high levels of HDLc may be associated with a higher risk of mortality in this group of patients [23].

Prospects for further research. Future research could investigate the specific mechanisms through which T2DM influences mortality in acute coronary syndrome patients, exploring potential therapeutic interventions or preventive measures targeting this population.

Limitations of the study. This study is limited by its retrospective design and relatively small sample size. Future studies with larger sample sizes and prospective designs could provide further insights into the relationship between female sex, T2DM, and in-hospital mortality in acute coronary syndrome patients. Additionally, the study did not explore potential confounding factors such as comorbidities or medication use, which could impact the observed associations. Addressing these limitations in future research could enhance the validity and generalizability of the findings.

Conclusion

No significant association was found between elevated HDL levels and in-hospital mortality. Although older age and the presence of T2DM were identified as significant risk factors, the analysis did not support a clear causal relationship between HDL levels and clinical outcome. These findings highlight the complexity of the interaction between HDL and cardiovascular disease, underscoring the need for additional research to better understand the underlying mechanisms and develop more effective therapeutic strategies.

Relationships and Activities: none.

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