Original Research

# The Impact of Gender and Race When Using the GRACE ACS Score to Predict Mortality

Ikechukwu Ogbu, MD[1]; Napatkamon Ayutyanont, PhD[2]; Sarah Wilson, MS[2]; Hossein Akhondi, MD[3]

Author affiliations are listed at the end of this article.

Correspondence to:
Ikechukwu Ogbu, MD
MountainView Hospital
2880 N Tenaya Way
2nd Floor
Las Vegas NV 89128
(iogbu832267@gmail.com)

## Abstract

### Background
Acute coronary syndrome (ACS) causes significant global morbidity and mortality and requires early risk stratification. The global registry of acute coronary events (GRACE) score is a well-known, validated risk stratification system that does not include race and gender. We aimed to assess whether the addition of gender and race could add to the predictability of the GRACE score model.

### Methods
We performed a retrospective cohort study of 46 764 ACS patients from the files of a national healthcare system. We compared the predictability of the GRACE score in conjunction with gender and race versus the original GRACE score. Different possible associations of predictability were investigated and statistically calculated. The accuracy of the prediction models was assessed using the receiver operating characteristic curve and its respective area under the curve (AUC). We compared the AUC of the 2 models, with the significance set at a *P* value of less than .05.

### Results
Our comparison favored the original GRACE score over the modified prediction model with gender and race added (AUC = 0.838 and 0.839 respectively, *P* = .008). Although the P value comparing the AUC shows that the original GRACE was superior, due to our large dataset, the actual numbers are similar and may not be clinically significant.

Gender and race were significantly associated with in-hospital mortality (*P* < .001, *P* = .002, respectively). However, this relationship disappeared in the multivariate analysis. Gender significantly predicted in-hospital mortality, with females 1.167 times more likely to die (*P* < .001). Non-white racial groups had lower in-hospital mortality than whites (OR: 0.823, *P* = .03).

### Conclusion
The GRACE score was valid in its original form and its ability to predict mortality was not substantially improved by including gender and race.

### Keywords
GRACE score; gender impact; race impact; acute coronary syndrome; hospital mortality; health status disparities; acute coronary syndrome; hospital mortality; heart diseases; Global Registry of Acute Coronary Events

## Introduction
Cardiovascular diseases are the most frequent cause of death globally, accounting for 32% of all deaths (over 17 million deaths in 2019).[1] Specifically, acute coronary syndrome (ACS) is responsible for a significant portion of deaths. Each year, about 605 000 individuals in the United States experience a new episode of ACS, and 200 000 others experience a recurrence.[2] ACS is a spectrum of disorders that

includes ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The leading cause of ACS is coronary atherosclerosis.[3,4]

ACS is frequently associated with poor prognosis, recurrence, or death.[5] The clinician needs to perform an early risk stratification to assign aggressive treatment for those at high risk or with poor prognoses.[6] Various scoring systems are currently available for this purpose, which utilize data from the patient's medical history, clinical examination, and laboratory/radiologic investigations.

The Global Registry of Acute Coronary Events (GRACE) was a prospective international registry that included over 40 000 patients with ACS, from which the GRACE risk prediction score was developed. The GRACE score is a validated model that can predict mortality risk following ACS (including STEMI, NSTEMI, and UA)[7,8] and can be used by inpatient clinicians to risk-stratify patients. Although it was developed in 2003, the international guidelines still recommend this scoring system, emphasizing its relevance. Clinicians can use the GRACE ACS score to risk-stratify patients at the time of presentation.[9] The 8 parameters considered in this scoring system are age, heart rate/pulse, systolic blood pressure (BP), ST-segment deviation on electrocardiogram (EKG), cardiac arrest at admission, serum creatinine, elevated cardiac enzymes, and Killip class for heart failure, generating a total score ranging from 2 to 372.[8] A score of less than 109 is low risk, between 109-140 is an intermediate risk, and greater than 140 is high-risk for in-hospital mortality. Therefore, patients with higher scores are considered high risk and could benefit from early revascularization therapy.[8]

Several studies have shown that women with ACS tend to have higher mortality rates than men.[10-13] This higher risk could be attributed to the more frequent comorbidities in these women.[14,15] Moreover, ethnic disparities in prognosis were also reported.[16] Although mortality risk is reported to vary by gender and race, these 2 parameters are not considered in the GRACE scoring system. Therefore, we aimed to compare the predictability of the original GRACE score versus a modified one incorporating gender and race. Additionally, this study aimed to calculate the risk of in-hospital mortality across different racial groups and genders.

## Methods

### Study Design and Sample

This is a retrospective cohort study of patients diagnosed with ACS with an electrocardiogram (EKG) performed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Institutional review board exemption was obtained after review by the HCA Healthcare Institutional Review Board manager system. All collected data and patient information were de-identified before analysis.

All patients in the HCA Healthcare system database (180 hospitals) across the continental United States between January 1, 2019, and December 31, 2019, were considered for eligibility. We included adult patients (more than 18 years old) who presented to the hospital and were diagnosed with ACS. The ACS diagnosis was based on EKG changes (ST-segment elevation of more than 0.2 mm or depression of more than 0.5 mm) and elevated troponin levels (> 0.045 ng/ml). Patients with significant comorbidities such as anemia, hyperthyroidism, sepsis, or trauma were excluded since the ailment could have affected EKG or troponin.

We queried electronic records for admission, discharge, inpatient medication, and billing records for information such as age, gender, and race (self-report). Race options were White, Black, Asian, American Indian, and other. We also collected systolic blood pressure (BP), heart rate/pulse, creatinine and troponin levels, EKG changes (ST-segment elevation or depression), aspirin use, clinical examination findings (jugular vein distension, rales, pulmonary congestion, cardiogenic shock or heart failure, and cardiac arrest at admission), mortality, and imaging reports (pulmonary vascular congestion on chest X-ray). We calculated a GRACE score for each patient.

### Measures

In-hospital mortality was the primary outcome of interest. We investigated in-hospital mortality by gender and race. Additionally, we compared the GRACE score between males

and females. To test our hypothesis on predictability, we compared the predictability of the GRACE score in conjunction with gender and race versus the original GRACE score.

### Statistical Analysis

We calculated our sample size based on findings by Berger et al in 2009 on gender as a risk factor for ACS mortality.[13] A total of 15 300 patients were required (7650 per gender) to achieve a 10% relative precision and 90% confidence interval.

Data were analyzed using the Statistical Analysis Software (SAS) version 9.4. Descriptive data were summarized as mean ± standard deviation (SD) for continuous variables and frequency with the proportion (%) for categorical variables. We used the independent sample t-test to compare the GRACE score between males and females. Additionally, the chi-square test was used to assess the association between in-hospital mortality and gender and between in-hospital mortality and race. Finally, 2 logistic regression models were run. One model included the original 8 parameters of the GRACE score, and another had the GRACE score with gender and race as covariates. The accuracy of the prediction models was assessed using the receiver operating characteristic (ROC) curve and its respective area under the curve (AUC). We compared the AUC of the 2 models, with the significance set at a *P* value less than .05.

## Results

Baseline characteristics of 103 309 patients' records in the HCA Healthcare database system were examined for eligibility. We included 46 764 eligible ACS patients in our cohort. The majority of our patients were male (60.85%). The White population was also predominant (73.59%), followed by the Black population (14.14%). The patients' age ranged from 18 to 90 years, with a mean of 66.2 ± 14.1. Most of our patients were in Killip class I (87.65%). Detailed baseline characteristics of the studied patients are provided in **Table 1**.

**Table 1.** Baseline Characteristics of the Studied Patients

| Variable | | All patients (N = 46 764) |
|---|---|---|
| Male gender | | 28 457 (60.85%) |
| Age (years) | | 66.2 ± 14.1 |
| Mean Weight (kg) | | 86 ± 68.5 |
| Race | White | 34 415 (73.59%) |
| | Black | 6614 (14.14%) |
| | Hawaiian/Asian | 803 (1.72%) |
| | American Indian | 414 (0.89%) |
| | Others | 4518 (9.66%) |
| Mean heart rate/pulse (beat/min) | | 85 ± 21.8 |
| Mean first systolic blood pressure (mmHg) | | 147 ± 32.0 |
| Electrocardiogram changes | | 32 282 (69.03%) |
| Left bundle branch block | | 4077 (8.72%) |
| Mean first creatinine level (mg/dL) | | 2.05 ± 4.1 |
| Kilip class | 1 | 40 990 (87.65%) |
| | 2 | 3749 (8.02%) |
| | 3 | 2025 (4.33%) |
| Cardiac arrest | | 1155 (2.47%) |
| Comorbidities (diabetes mellitus/hypertension/angina) | | 22 632 (48.4%) |
| Aspirin use | | 27 308 (58.4%) |
| Underwent echocardiography | | 37 050 (79.23%) |

Data are presented as frequency (%) or mean ± standard deviation.

**Table 2.** Mortality in Each Racial Group

| Race | Mortality | | |
|---|---|---|---|
| Frequency<br>Percent<br>Row Percentage<br>Column Percentage | 0 | 1 | Total |
| **American Indian** | 388 | 26 | 414 |
| | 0.83 | 0.06 | 0.89 |
| | 93.72 | 6.28 | |
| | 0.88 | 0.94 | |
| **Black** | 6289 | 325 | 6614 |
| | 13.45 | 0.69 | 14.14 |
| | 95.09 | 4.91 | |
| | 14.30 | 11.69 | |
| **Hawaiian/Asian** | 745 | 58 | 803 |
| | 1.59 | 0.12 | 1.72 |
| | 92.78 | 7.22 | |
| | 1.69 | 2.09 | |
| **Other** | 4236 | 282 | 4518 |
| | 9.06 | 0.60 | 9.66 |
| | 93.76 | 6.24 | |
| | 9.63 | 10.15 | |
| **White** | 32 327 | 2088 | 34 415 |
| | 69.13 | 4.46 | 73.59 |
| | 93.93 | 6.07 | |
| | 73.50 | 75.13 | |
| **Total** | 43 985 | 2779 | 46 764 |
| | 94.06 | 5.94 | 100.00 |

Compared to males, females had higher GRACE scores (-3.76 ± 1.48 vs. -3.61 ± 1.45, respectively). This difference was statistically significant ($P < .001$). Among the 46 764 studied ACS patients, 2779 died within 30 days, representing 5.94% of the studied patients (Table 2). In-hospital mortality was higher in females (n = 1207, 6.59%) than in males (n = 1572, 5.52%; $P < .001$). Logistic regression revealed that females were 1.167 (95% CI [1.074 to 1.268]) times more likely to die than males.

Regarding race, a significant difference in the distribution of in-hospital mortality was observed across the different ethnic groups ($P = .002$, **Table 2**). Being from the non-White population predicted less in-hospital mortality. Non-Whites had a 0.823 (95% CI [0.712 to 0.951]) likelihood of in-hospital mortality when compared to White patients (**Table 3**). At the 95% CI, the female gender and the White population were significantly associated with in-hospital mortality ($P < .001$ and P = .030, respectively).

When combined with gender and race, the GRACE score was a significant predictor of in-hospital mortality ($P < .001$). The AUC for this modified risk prediction model was 0.838 (95% CI [0.832 to 0.847]), indicating excellent accuracy. However, using the original GRACE score model resulted in a slightly larger AUC (0.839, 95% CI [0.830 to 0.845]), meaning the original score was better at predicting in-hos-

**Table 3.** Effect of Gender and Race on Mortality in a Univariate Analysis

| Variable | OR | 95% CI | *P* value |
|---|---|---|---|
| **Gender** | | | |
| Males | Reference | | |
| Females | 1.167 | 1.074-1.268 | .0003 |
| **Race** | | | |
| White | Reference | | |
| American Indian | 1.068 | 0.695 - 1.640 | .6064 |
| Black | 0.880 | 0.773 - 1.002 | .1667 |
| Hawaiian/Asian | 1.135 | 0.850 - 1.516 | .2241 |
| Other | 0.823 | 0.712 - 0.951 | .0296 |

Abbreviations: CI = confidence interval, OR = odds ratio

pital mortality. The difference between these two prediction models was statistically significant ($P$ = .008) (**Figure 1**).

## Discussion

We have presented a retrospective cohort study that focused on the impact of gender and race in predicting the risk of in-hospital mortality following an ACS episode. We assessed the predictability of our modified model that included the conjunction of the GRACE score with gender and race. Our new, modified model was a significant predictor of in-hospital mortality ($P$ < .001), with an AUC of 0.839, indicating excellent accuracy. However, when compared to the original GRACE score, a significant statistical difference was detected ($P$ = .008) in favor of the original score, meaning that the

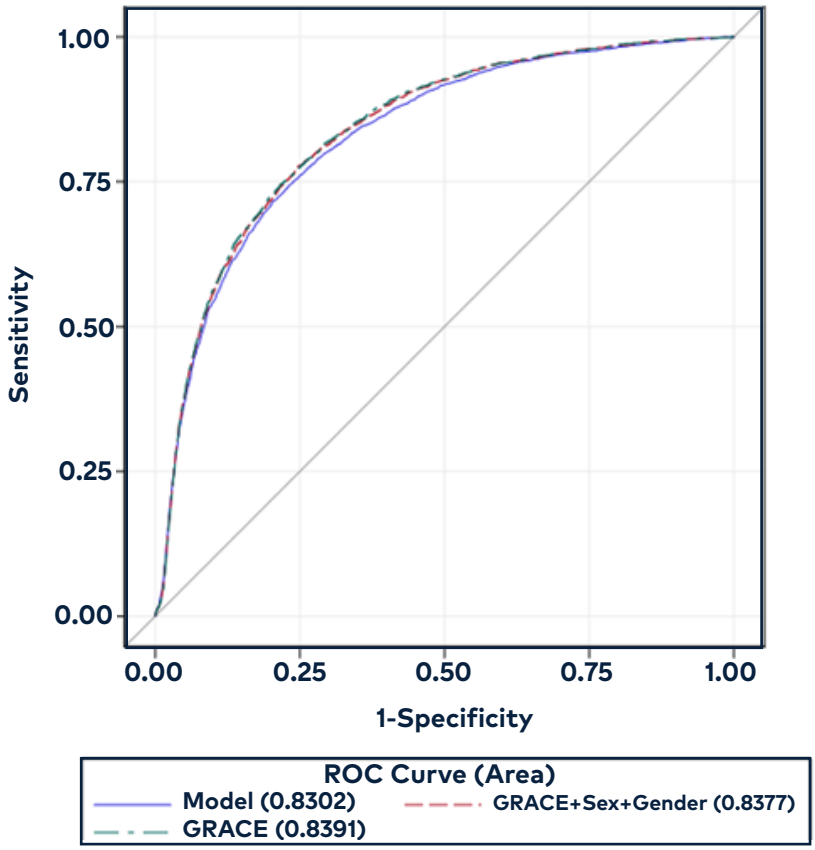


**Figure 1.** ROC curves compare the GRACE and the conjoint GRACE scores with gender and race.

addition of race and gender did not help with the prediction.

A gender disparity was observed in our cohort. This finding of higher mortality in females with ACS was consistent with previous studies by Gong et al in 2017[17] and Cabrerizo-García et al in 2015.[11] Several factors were suggested to result in this significant difference. Due to the protective effect of estrogen—an effect lost after menopause—women tend to present with more severe ACS at an older age when compared to men.[11,18] Additionally, this difference might be attributed to the associated comorbidities and risk factors. Several studies on ACS patients reported a higher prevalence of hypertension, diabetes mellitus, and dyslipidemia among women.[11,19-21] Hypertension is a well-known cause of left ventricular hypertrophy, an entity that worsens the prognosis of ACS.[22] Diabetes has various harmful effects on the coronary vasculature resulting in heart failure and poor prognosis.[23] These differences in the baseline characteristics could be supported by the fact that females had significantly higher GRACE scores at presentation. A finding that was consistent with previous studies.[11-17]

A significant association was detected between race and mortality, a finding also reported by Yong et al in 2018.[16] In our cohort, being from the non-White population predicted a lower likelihood of mortality in comparison with the White population. Yong et al in 2018 also reported a better prognosis for Black patients than White patients.[16] Additionally, Musey et al in 2017 reported better outcomes with non-White patients.[24] Different races can have other associated comorbidities and different responses to certain drugs.[25,26]

Although our modified prediction model was deemed accurate, it was not superior to the original GRACE score. This indicates that the significant predictability of adding gender and race for mortality disappeared in the multivariate analysis. The same results were reported in the predictability model of Cabrerizo-García et al who combined the GRACE score with gender.[11] As the GRACE score measures the baseline characteristics, this difference in mortality across gender and racial groups could be related to a difference in the treatment they receive.

Our findings add to the ongoing research on the effects of race and gender on different aspects of medicine. From the implicit gender bias when using various cardiac testing modalities, the impact of race and gender on C-reactive protein, the influence of race and gender in the care process, resource use, and outcomes in heart failure; gender and race issues have been subjected to extensive analysis.[27-29] Although there are some disparities and differences in some areas, the GRACE score appears to be most effective at predicting outcomes when not factoring race and gender.

Although GRACE has been proposed for updates in the past[30], it was through modifying non-linear associations versus linear ones or using an electronic version rather than the computation of a numerical score. Also, creatinine and Killip scores were substituted to ease use.[30] Some authors have proposed improved risk stratification of GRACE with the addition of pro-B-type natriuretic peptide and C-reactive protein.[31] Others have suggested GRACE adjustment by adding growth differentiation factor 15.[32] However, it seems that the original GRACE remains the most effective predictor.

Our study is the first to assess the GRACE score's predictability in conjunction with gender and race among ACS patients. We included patients from different racial groups representing varied populations. However, as this study was retrospective in its design, we relied on the data available on patients' records, which can be defective and misleading and limit our ability to adjust for the confounders.

## Conclusion

Our modified GRACE prediction model that included gender and race was a significant predictor of in-hospital mortality with excellent accuracy. However, the modified GRACE score had somewhat slightly lower predictive power than the original GRACE score.

Gender and race were significantly related to in-hospital mortality for patients with ACS. Females had a greater likelihood of death than males, and non-White populations have a lower chance of death than the White population.

## Conflicts of Interest

The author declares that they have no conflicts of interest.

Dr Ogbu is an employee of MountainView Hospital, a hospital affiliated with the journal's publisher.

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## Author Affiliations

1. MountainView Hospital, Las Vegas, NV
2. HCA Healthcare Graduate Medical Education, Brentwood, TN
3. Universal Health Services, Las Vegas, NV

## References

1. Cardiovascular diseases (CVDs). World Health Organization (WHO); 2021. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics - 2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743. doi:10.1161/CIR.0000000000000950
3. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. *Circulation*. 2003;108(14):1664-1672. doi:10.1161/01.CIR.0000087480.94275.97
4. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation*. 2001;103(7):934-940. doi:10.1161/01.cir.103.7.934
5. Zandecki L, Janion-Sadowska A, Kurzawski J, et al. Clinical presentation and 3-year outcomes of patients with acute coronary syndromes and non-obstructive coronary arteries on angiography. *PLoS One*. 2020;15(6):e0234735. doi:10.1371/journal.pone.0234735
6. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2165-2175. doi:10.1056/NEJMoa0807986
7. Goodman SG, Huang W, Yan AT, et al. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. *Am Heart J*. 2009;158(2):193-201.e2015. doi:10.1016/j.ahj.2009.06.003
8. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163(19):2345-2353. doi:10.1001/archinte.163.19.2345
9. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
10. Bennett SK, Redberg RF. Acute coronary syndromes in women: is treatment different? Should it be?. *Curr Cardiol Rep*. 2004;6(4):243-252. doi:10.1007/s11886-004-0071-2
11. Cabrerizo-García JL, Pérez-Calvo JI, Zalba-Etayo B. Influence of gender on prognosis of acute coronary syndromes. *Rev Port Cardiol*. 2015;34(1):43-50. doi:10.1016/j.repc.2014.07.008
12. El-Menyar A, Ahmed E, Albinali H, et al. Mortality trends in women and men presenting with acute coronary syndrome: insights from a 20-year registry. *PLoS One*. 2013;8(7):e70066. doi:10.1371/journal.pone.0070066
13. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. *JAMA*. 2009;302(8):874-882. doi:10.1001/jama.2009.1227
14. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307(8):813-822. doi:10.1001/jama.2012.199
15. Goldberg RJ, O'Donnell C, Yarzebski J, Bigelow C, Savageau J, Gore JM. Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. *Am Heart J*. 1998;136(2):189-195. doi:10.1053/hj.1998.v136.88874
16. Yong CM, Ungar L, Abnousi F, Asch SM, Heidenreich PA. Racial differences in quality of care and outcomes after acute coronary syndrome. *Am J Cardiol*. 2018;121(12):1489-1495. doi:10.1016/j.amjcard.2018.02.036
17. Gong IY, Goodman SG, Brieger D, et al. GRACE risk score: sex-based validity of in-hospital mortality prediction in Canadian patients with acute coronary syndrome. *Int J Cardiol*. 2017;244:24-29. doi:10.1016/j.ijcard.2017.06.055
18. Jneid H, Thacker HL. Coronary artery disease in women: different, often undertreated. *Cleve Clin J Med*. 2001;68(5):441-448. doi:10.3949/ccjm.68.5.441

19. Galappatthy P, Bataduwaarachchi V, Ranasinghe P, et al. Sex difference in risk factors, GRACE scores, and management among post-acute coronary syndrome patients in Sri Lanka. *Cardiol Res Pract*. 2020;2020:4560218. doi:10.1155/2020/4560218
20. Cooney M, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: first report of an international audit. *Eur J Prev Cardiol*. 2014;21(7):813-822. doi:10.1177/2047487312467870
21. Hemal K, Pagidipati NJ, Coles A, et al. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *JACC Cardiovasc Imaging*. 2016;9(4):337-346. doi:10.1016/j.jcmg.2016.02.001
22. Coca A, Cea-Calvo L, Lozano JV, et al. High-density lipoprotein cholesterol and cardiovascular disease in Spanish hypertensive women. The RIMHA study. *Rev Esp Cardiol*. 2009;62(9):1022-1031. doi:10.1016/s1885-5857(09)73268-2
23. Severino P, D'Amato A, Pucci M, et al. Ischemic heart disease and heart failure: role of coronary ion channels. *Int J Mol Sci*. 2020;21(9):3167. doi:10.3390/ijms21093167
24. Musey PI Jr, Kline JA. Do gender and race make a difference in acute coronary syndrome pretest probabilities in the emergency department?. *Acad Emerg Med*. 2017;24(2):142-151. doi:10.1111/acem.13131
25. Cresci S, Dorn GW 2nd, Jones PG, et al. Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. *J Am Coll Cardiol*. 2012;60(10):898-907. doi:10.1016/j.jacc.2012.02.051
26. Hasan MS, Basri HB, Hin LP, Stanslas J. Genetic polymorphisms and drug interactions leading to clopidogrel resistance: why the Asian population requires special attention. *Int J Neurosci*. 2013;123(3):143-154. doi:10.3109/00207454.2012.744308
27. Daugherty SL, Blair IV, Havranek EP, et al. Implicit gender bias and the use of cardiovascular tests among cardiologists. *J Am Heart Assoc*. 2017;6(12):e006872. doi:10.1161/JAHA.117.006872
28. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol*. 2005;46(3):464-469. doi:10.1016/j.jacc.2005.04.051
29. Philbin EF, DiSalvo TG. Influence of race and gender on care process, resource use, and hospital-based outcomes in congestive heart failure. *Am J Cardiol*. 1998;82(1):76-81. doi:10.1016/s0002-9149(98)00233-1
30. Fox KA, Fitzgerald G, Puymirat E, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open*. 2014;4(2):e004425. doi:10.1136/bmjopen-2013-004425
31. Klingenberg R, Aghlmandi S, Räber L, et al. Improved risk stratification of patients with acute coronary syndromes using a combination of hsTnT, NT-proBNP and hsCRP with the GRACE score. *Eur Heart J Acute Cardiovasc Care*. 2018;7(2):129-138. doi:10.1177/2048872616684678
32. Widera C, Pencina MJ, Meisner A, et al. Adjustment of the GRACE score by growth differentiation factor 15 enables a more accurate appreciation of risk in non-ST-elevation acute coronary syndrome. *Eur Heart J*. 2012;33(9):1095-1104. doi:10.1093/eurheartj/ehr444