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RESEARCH ARTICLE

Killip-Kimball classification in octogenarians with acute coronary syndrome: an 11-year experience

Clasificación de Killip-Kimball en octogenarios con síndrome coronario agudo: 11 años de experiencia

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Abstract

Objective: *The objective of the study is to validate the use of the Killip-Kimball classification (KC) as a predictor of outcomes in an octogenarian cohort with acute coronary syndrome.* **Methods:** *A retrospective analysis of patients who underwent a catheterization procedure for acute coronary syndrome (ACS) was performed. ACS was defined as per the American Heart Association guidelines, and included ST-elevation myocardial infarction (STEMI), non-STEMI and Unstable Angina. We determined factors associated with the KC upon admission to the emergency room. Likewise, we compared in-hospital mortality, length of stay, and other outcomes dividing the patients by KC.* **Results:** *A total of 133 patients with a mean age of 83 years were analyzed and assigned a KC from 1 to 4 according to clinical presentation. Each group included 86, 9, 23, and 15 patients, respectively. In-hospital mortality was 12%, 5% in KC-I, 11% in KC-II, 22% in KC-III, and 40% in KC-IV with a significant difference between classes (p = 0.002). In addition, we found higher KC groups to be associated with acute kidney injury during the hospitalization (p < 0.01).* **Conclusion:** *Despite a strong reduction in mortality for elderly patients with ACS in recent decades, patients presenting with ACS and higher KC have a high mortality rate, as described in younger cohorts. KC remains a reliable prognostic tool, with applicability in octogenarian patients.*

Keywords: *Killip-Kimball. Acute coronary syndrome. Octogenarian. Acute heart failure.*

Resumen

Objetivo: *Validar el uso de la clasificación de Killip- Kimball como predictor de desenlaces en una cohorte de pacientes octogenarios con síndrome coronario agudo.* **Métodos:** *Se realizó un análisis retrospectivo de pacientes sometidos a cateterismo por síndrome coronario agudo (ACS). Se incluyeron infarto al miocardio con y sin elevación del segment ST, así como angina inestable, utilizando las definiciones de la American Heart Association (AHA). Se determinaron los factores que influyeron en la clasificación de Killip-Kimball (KC) al momento de ingreso al hospital. Se comparó la mortalidad, la estancia intrahospitalaria y otros desenlaces, dividiendo a los pacientes por su KC.* **Resultados:** *Un total de 133 pacientes se incluyeron en el análisis y se clasificaron dependiendo de su KC (I-IV). Cada grupo incluyó 86, 9, 23 y 15 pacientes, respectivamente. La edad media fue de 83 años. La mortalidad intrahospitalaria fue de 5, 11, 22 y 40%, respectivamente para cada KC, y 12% global. Hubo una diferencia significativa en la mortalidad por clase (p = 0.002). Adicionalmente, se encontró que a mayor KC, mayor riesgo de lesión renal aguda durante la hospitalización (p < 0.01).* **Conclusión:** *A pesar de una reducción*

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en la mortalidad de adultos mayores con ACS en décadas recients, pacientes con ACS y mayor KC tienen riesgo aumentado de morir, igual que pacientes en grupos de edad menores. La KC continñua siendo una herramienta confiable para la clasificación y con utilidad pronóstica, con aplicabilidad en pacientes mayores de 80 años.

Palabras clave: *Killip-Kimball. Síndrome coronario agudo. Octogenario. Insuficiencia cardiaca aguda.*

Introduction

As the population around the world ages, chronic diseases become more prevalent. In particular, the prevalence of coronary artery disease has grown in the past few decades[1]. Hence, patients in the very elderly population with acute coronary syndrome (ACS) represent a higher proportion of admissions. Conventionally, octogenarian and nonagenarian patients with ACS were not treated with percutaneous coronary intervention (PCI), given the poor prognosis and the high risk of undergoing an invasive procedure. For these reasons, very elderly patients were excluded from clinical trials in light of standardizing treatment for ACS[2]. Nonetheless recent data suggest in-hospital morbidity and mortality do not differ greatly when compared with younger patients[3]. In 1967, Killip and Kimball published a classification that has been widely used as a clinical estimate of acute heart failure (AHF) severity in adults with ACS. Moreover, it assesses the risk of in-hospital death and potential benefit of care provided in Coronary Care Units. The Killip-Kimball Classification (KC) stratifies patients into four groups following the clinical criteria according to Killip and Kimball in their original paper. KC-I: no signs of congestion, KC-II: S3 heart sound and basal rales on auscultation, KC-III: acute pulmonary edema and KC-IV: cardiogenic Shock[4]. The clinical relevance of this classification is the short- and long-term mortality estimation; which several authors have attempted to define[3,5,6]. New scoring systems aiming to predict mortality with greater precision have emerged, although, the Killip classification remains an easy-to-use tool that has proven to be reliable. The aim of our study is to validate this classification method in patients who are 80 years or older in a developing country to facilitate treatment decisions and prognosis as well as an in-hospital predictor of outcomes.

Methods

We performed a retrospective analysis that included octogenarian and nonagenarian patients who underwent invasive treatment in either of two academic third-level centers in Mexico from January 2008 to April 2019. Approval of the pertained ethics committee was obtained accordingly. ACS was divided into three categories: acute ST-elevation myocardial infarction (STEMI), non-STEMI (non-STEMI), and unstable angina (UA). These diagnoses were assigned based on criteria according to the definitions of the American Heart Association guidelines[7,8]. KC category was retrospectively assigned based on the criteria mentioned above. The hospital's electronic medical record (EMR) was used to extract patient data and classify according to KC. Our primary aim is to estimate the association between KC and in-hospital mortality, given current medical and interventional management. Our secondary aim is to find other variables that are associated with a higher KC in our cohort, such as length of stay (LOS) and development of acute kidney injury (AKI).

Statistical analysis

Kolmogorov–Smirnov test was used to assess normality of distribution of continuous variables. Count data are reported as number (%), variables with a normal distribution are reported as mean (standard deviation [SD]), and non-parametric variables are reported as median (interquartile range [IQR]). Analysis of variance (ANOVA) and T-Student were used for normally distributed variables while Kruskal–Wallis and Mann–Whitney U were used for nonparametric, continuous variables. Post hoc testing included Tukey for ANOVA and Dunn's test for Kruskal-Wallis. We used an alpha of 0.05 to declare statistical significance in all of the tests performed. Statistical analysis was performed in SPSS v25 (Boston IBM) and R statistical software (version 3.6.1).

Results

A total of 193 participants were admitted with ACS and underwent cardiac catheterization. After excluding participants with an incomplete EMR, 133 patients were included for analysis. The population included 54 (40.6%) females and 79 (59.4%) males. Gender was not different between groups ($p = 0.4$). Median age was 83 (4) and was not statistically different between KC groups ($p = 0.4$).

Table 1. Baseline characteristics

Variables	KC-I	KC-II	KC-III	KC-IV	n	p-value
DM2	39 (45%)	2 (22%)	10 (44%)	7 (47%)	58 (44%)	0.607
HTN	62 (72%)	8 (89%)	17 (74%)	10 (67%)	97 (73%)	0.634
Smoking	25 (29%)	3 (33%)	8 (24.8%)	4 (27%)	40 (30%)	0.938
Dyslipidemia	34 (40%)	6 (67%)	7 (30%)	3 (20%)	50 (44%)	0.116
PVD	17 (20%)	1 (11%)	4 (17%)	3 (20%)	25 (19%)	0.931
AF	15 (17%)	2 (22%)	6 (26%)	1 (7%)	24 (18%)	0.485
Stroke	6 (7%)	3 (33%)	2 (9%)	3 (20%)	14 (11%)	0.054
CABG	17 (20%)	1 (11%)	3 (13%)	0 (0%)	21 (16%)	0.249
COPD	11 (13%)	1 (11%)	1 (4%)	2 (13%)	15 (11%)	0.707
CKD	8 (9%)	2 (22%)	4 (17%)	1 (7%)	15 (11%)	0.459

Fifty-eight patients (43.6%) had prior history of type 2 diabetes mellitus (DM2), while 96 (72.9%) had prior hypertension (HTN) history. Twenty-one (15.8%) had past medical history of CABG. Other cardiovascular comorbidities such as stroke were present in 14 (10.5%) of cases. No significant differences were found between KC groups of patient's prior history and comorbidities on admission including DM2, HTN, dyslipidemia, smoking, COPD, CKD, peripheral vascular disease (PVD), atrial fibrillation (AF), prior stroke, or CABG (Table 1).

Emergency department (ED) medical treatment was homogeneous between KC groups. Among all groups, 77 (42%) patients received P2Y12 antagonists ($p = 0.908$), with clopidogrel, prasugrel, or ticagrelor. Ninety-eight (74%) received anticoagulation ($p = 0.6$) with activated factor X inhibitors, unfractionated heparin, or low molecular weight heparin. Seventy-four (55%) received statin therapy ($p = 0.6$). Upon admission at the ED, 35 (26%) patients received beta blockers (BB) ($p = 0.3$), and 98 (74%) received aspirin therapy ($p = 0.6$). Although there was no significant difference regarding the treatment in the ED between groups, there was a trend toward a higher proportion of patients receiving BB as well as aspirin therapy in the KC-IV group.

STEMI was diagnosed in 34 (26%) patients, the remaining 99 patients had a diagnosis of either non-STEMI or UA. There was a significantly lower proportion of patients with STEMI in the KC-I category. Only 4 (3%) patients underwent CABG during their admission after unsuccessful PCI attempt or unfavorable coronary anatomy to interventional revascularization at the discretion of the interventional cardiologist. A total of 92 (69%) patients had at least 1 stent deployed. Nonetheless, stent placement was not different between groups ($p = 0.8$).

Baseline characteristics

No significant differences were found between KC groups of patient's prior history and comorbidities on admission including DM2, HTN, dyslipidemia, smoking, COPD, CKD, PVD, AF, prior stroke, or CABG. Findings are summarized in table 1.

Admission laboratory values and hemodynamic parameters

Median creatine phosphokinase (CPK) was 102.5 mg/dl. Significant differences were found between groups in CPK values ($p < 0.01$) with differences present between groups KC-I and III ($p < 0.01$), and KC-I and IV ($p < 0.01$). Median CPK muscle-brain (CK-MB) was 24 mg/dl, with significant difference between groups ($p < 0.01$). Particularly between KC-I and IV ($p = 0.01$). Mean hemoglobin (Hb) was 12.4 mg/dl, with no differences found between groups ($p = 0.4$). Median glucose on admission was 138.5, and statistically different between groups ($p < 0.01$), particularly between KC-II and III ($p = 0.02$) and KC-II and IV ($p = 0.02$). Median creatinine was 1.81mg/dl, and significantly different between groups ($p < 0.01$) and with differences present between KC-I and KC-IV ($p < 0.01$) and KC-II and KC-IV ($p < 0.01$). Mean leukocyte count was

Table 2. Admission laboratory values and hemodynamic parameters.

Variables	Units	KC-I	KC-II	KC-III	KC-IV	p-value
CPK*	mg/dl	86 (161)	122 (817)	100 (857)	598 (684)	< 0.001
CK-MB*	mg/dl	21.8 (23.2)	33 (83.3)	23 (81.7)	35 (73.8)	< 0.01
Hb*	mg/dl	12.2 (3.1)	12 (0.5)	12.5 (2.5)	12.9 (2.3)	0.442
*Leucocytes^*	10^3/μL	9,322 (3,746)	8,620 (2,050)	11,664 (4,031)	13,058 (4,466)	< 0.001
Glucose*	mg/dl	140 (68)	102 (82.7)	159 (135)	165 (110.5)	< 0.01
Creatinine*	mg/dl	1.0 (0.5)	0.95 (45)	1.2 (0.6)	1.86 (0.97)	< 0.001
*SBP^*	mmHg	124 (20)	116 (16)	131 (37)	93 (25)	< 0.001
*DBP^*	mmHg	74 (16)	63 (13)	73 (18)	61 (12)	< 0.001
*HR^*	bpm	81 (14)	73 (17)	104 (32)	96 (36)	< 0.001
LVEF*	%	55 (15)	50 (18)	40 (30)	30 (10)	0.005

*Median (IQR); ^Mean (SD)

10,382/μL with statistical significance between groups ($p < 0.01$). Differences between KC-I versus III ($p < 0.01$), and KC-I versus IV ($p < 0.01$) were significant.

As far as hemodynamic parameters, admission left ventricular ejection fraction (LVEF), Heart Rate (HR), SBP, and Diastolic blood pressure (DBP) blood pressures were analyzed for each group. Median HR was 84 bpm, significantly different between KC groups. Subgroup analysis revealed statistical significance between KC-I and III ($p < 0.01$) as well as KC-I and IV ($p < 0.01$). As for SBP with a mean of 126 mmHg, groups were statistically different ($p < 0.01$). In subgroup analysis, there were significant differences between KC-I and IV ($p < 0.01$). Mean DBP was 73 mmHg, significantly different among groups ($p < 0.01$). In subgroup analysis, KC-I and IV ($p < 0.01$) were significantly different. Median LVEF was 50%, significantly lower in KC-IV compared to KC-I ($p = 0.005$). KC-I and III were also significantly different ($p = 0.026$). Admission laboratory values and hemodynamic parameters for each KC group are enlisted in table 2.

Electrocardiographic characteristics in the ED

Admission electrocardiograms were assessed for abnormalities. AV node blocks and ST segment elevations were significantly different among KC I and III. However, only AV block was significantly higher in KC IV compared to KC I. Findings of all ECG characteristics are summarized in table 3.

Primary aim

A total of 16 (12%) patients died during hospitalization. Four (5%) in KC-I, 1 (11%) in KC-II, 5 (22%) in KC-III, and 6 (40%) in KC-IV. Mortality was significantly different among classes ($p < 0.01$), with subgroup significant differences between KC-I and III ($p < 0.01$) as well as for KC-I and IV ($p < 0.01$).

Exploratory analysis

A total of three patients suffered a stroke episode during the hospitalization, two (9%) in the KC-III group and one (7%) in the KC-IV group. A total of 4 patients suffered reinfarction in our cohort, one (1%) in KC-I, one (4%) in KC-III, and two (13%) in KC-IV. Thirty-three patients were documented to have any degree of AKI, 13 (15%) in KC-I, 1 (11%) in KC-II, 11 (48%) in KC-III, and 8 (53%) in KC-IV. While no differences were found between reinfarction rates and stroke between KC groups, significant differences were found in development of intra-hospital AKI between groups As for Systolic blood pressure (SBP) with a mean of 119 mmHg, groups were statistically different ($p < 0.001$). In subgroup analysis, there were significant differences between KC-I and IV ($p < 0.001$). Incident AKI was significant between KC-I and III ($p <0.01$), as well as KC-I and IV ($p < 0.01$), even after adjusting for previous CKD. Median length of stay was 4 days (IQR 4.3). Excluding patients with a fatal outcome, LOS between KC groups was statistically significant ($p < 0.01$), with differences found between KC-I and K-IV ($p < 0.05$).

Table 3. Electrocardiogram findings. Count (proportion)

Variables	KC-I	KC-II	KC-III	KC-IV	n	p-value
Sinus Rhythm	45 (52%)	5 (56%)	18 (82%)	9 (60%)	77 (58%)	0.097
ST Elevation	12 (14%)	4 (44%)	12 (52%)	6 (40%)	34 (26%)	< 0.01
TWA	40 (47%)	2 (22%)	8 (35%)	4 (27%)	54 (41%)	0.258
AV Block	21 (25%)	4 (44%)	4 (17%)	11 (73%)	49 (37%)	< 0.01
LBBB	13 (15%)	2 (22%)	3 (13%)	3 (20%)	21 (16%)	0.892

AV: atrioventricular; KC: Killip-Kimball Classification; LBBB: left bundle branch block; TWA: t-wave abnormality.

Discussion

The prognosis of the very elderly patients after ACS has improved, largely due to refinement of medical treatment and PCI protocols[9-11]. A recent meta-analysis that included 32 studies corroborated the importance of prioritizing PCI in patients admitted for STEMI, where they found a relative risk of 1.52 of short-term mortality in patients with > 90 min of door-balloon time compared to those with < 90 min of door-balloon time[12]. These results included but were not limited to elderly patients. Among causes of death in the very elderly population with ACS, cardiogenic shock, and acute renal failure are the most prevalent culprits reported[13]. Despite the KC being classic and simple, research around it has prevailed and many centers continue to use it for clinical profile classification purposes. A landmark contribution recently made in 2019 by Zadok and collaborators demonstrated statistical significance in both short- and long-term mortality in patients with higher KC. In their cohort's large sample size, the added value of following patients for a longer period of time demonstrated that higher KC was associated with an increased mortality rate at 1 year[5]. This is a meaningful contribution since KC has been traditionally used in the acute setting and not necessarily meant to be used as a mid- or long-term mortality predictor. Consistent with this publication, a study done by DeGeare and colleagues in 2001 found, in a large cohort, a significant association between KC and 6-month mortality, although excluding participants in class IV. Our study showed consistent results with the other cohorts in developed countries. Our results, based on a multicenter cohort in a developing country, found robust evidence regarding the use of the KC in the setting of ACS in patients 80 years or older. In concordance with recent data, this study strengthens the prognostic value, as well as the clinical implications of the routine implementation of this classification. The overall mortality in our population was 8% before excluding patients with incomplete EMR, after which the mortality rose to a more overwhelming 12%. Hence, the results obtained from this study in octogenarians and nonagenarians, shows very similar mortality rates within each clinical profile compared to studies with younger cohorts[3]. Our findings pertaining hemodynamic measurements were as expected. By definition, KC-IV must have shock, which is frequently associated with tachycardia and decreased SBP and DBP, as worsening systolic function and consequent activation of compensatory mechanisms[14,15]. Thus, we analyzed these results to provide insight on the degree of hemodynamic compromise as well as to have LVEF as another point of reference. Akin to the previous literature, higher KC tended toward higher HR, although this is an expected finding owed to compensatory mechanisms.

These findings further solidify the decision to aggressively treat elderly patients with ACS, rather than utilizing a conservative approach as well as determine a more reliable prognosis after an interventional procedure[16,17]. Our study strengthens the growing literature supporting the use of KC as an in-hospital mortality prognostic indicator, including in the very elderly population. In addition, we describe how this classification relates to other paraclinical studies and laboratory values. In spite of a population from a developing country, our patients had an acceptable Hb concentration among all groups. This finding reflects an overall wellness status within the study cohort. Global renal function was reduced, with a median creatinine of 1.81 mg/dl during admission. This rather expected finding could be partially explained by the ACS insult and reflects the important association between renal disease and cardiovascular disease.

Utilizing all this information in conjunction may give a much clearer picture and expectation of the very elderly patient's clinical scenario. In addition, it validates the use of the KC in this particular population, thus supporting clinicians predict in-hospital outcomes.

Limitations

The retrospective nature of our study cohort renders potential hidden confounders that could not have been taken into account. Our database consisted of patients who underwent cardiac catheterization. As a result, patients deceased at the ED or if the attending physician decided to exclusively use medical treatment were not included in this cohort, this limitation has potential implications on underestimating the severity of ACS in our population. The treatment strategy was at the discretion of the attending cardiologist, making our cohort heterogeneous in terms of interventions. As both centers included in the study are third level, there is limited generalizability toward the whole octogenarian and nonagenarian community, depending on the accessibility to healthcare facilities. Moreover, a limited number of patients in some of the KC groups may have impeded the rejection of null hypotheses in this study.

Conclusion

In recent decades, the population has transitioned toward an older demographic. Newer and better therapies quickly emerge. This will inevitably lead to an increased prevalence of cardiovascular diseases, mandating the development of quality evidence in this population to develop effective treatment strategies in light of mitigating the mortality rate. Our study adds evidence to the scanty literature describing short-term mortality in octogenarian patients with ACS. The KC has good prognostic value for the very elderly population and has proven a good tool to reliably stratify patients according to their clinical profile. These new insights to the use of the KC in this population should help clinicians have a better sense of the outcomes of octogenarian patients with ACS in the ED. We encourage new initiatives to further polish the prognostic value of this classification in the current era with controlled studies to define better and more personalized risk-benefit treatment schemes for this growing population.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

The authors declare that due to the retrospective nature of the study, informed consent was waived. Study procedures were performed according to the delarations of Helsinki.

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