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# Electrocardiographic Findings in Patients with Acute Coronary Syndrome Presenting with Out-of-hospital Cardiac Arrest

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**Running head:** ECG findings in ACS with OHCA

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**Abstract**

We sought to characterize presenting electrocardiographic findings in patients with acute coronary syndromes (ACS) and out-of-hospital cardiac arrest (OHCA). In the Global Registry of Acute Coronary Events (GRACE) and Canadian ACS Registry I, we examined presenting and 24-48 hour follow-up ECGs of ACS patients who survived to hospital admission, stratified by presentation with OHCA. We assessed the prevalence of ST-segment deviation and bundle branch blocks and their association with in-hospital and 6-month mortality amongst those with OHCA. 215 (1.8%) of 12,040 ACS patients survived to hospital admission following OHCA. Those with OHCA had higher presenting rates of ST-segment elevation, ST-segment depression, T wave inversion, precordial Q waves, left bundle branch block (LBBB), and right bundle branch block (RBBB) than those without. Among patients with OHCA, those with ST-segment elevation had significantly lower in-hospital mortality (20.9% vs. 33.0%, p=0.044) and a trend toward lower 6-month mortality (27% vs. 39%, p=0.060) compared to those without ST-segment elevation. Conversely, among OCHA patients, LBBB was associated with significantly higher in-hospital and 6-month mortality rates (58% vs. 22%, p<0.001 and 65% vs. 28%, p<0.001 respectively). ST-segment depression and RBBB were not associated with either outcome. 63% of bundle branch blocks (RBBB or LBBB) on the presenting ECG resolved by 24-48 hours. In conclusion, compared with ACS patients without cardiac arrest, those with OHCA had higher rates of ST-segment elevation, LBBB and RBBB on admission. Among OHCA patients, ST-segment elevation was associated with lower in-hospital mortality, while LBBB was associated with higher in-hospital and 6-month mortality.

**Key words:** Acute coronary syndrome, out-of-hospital cardiac arrest, electrocardiogram

## INTRODUCTION

Previous studies have established the importance of early ECG assessment in out-of-hospital cardiac arrest (OHCA) to help identify patients with acute coronary syndromes (ACS). ECGs are used to triage patients for immediate cardiac catheterization[1] and in this setting, ECG diagnostic criteria for ST-segment elevation myocardial infarction identify a culprit coronary lesion with a positive predictive value >80%[2-5]. Moreover, immediate coronary angiography and percutaneous coronary intervention (PCI) in patients with OHCA and an occluded coronary artery improves outcomes[6]. ST-segment elevation may therefore suggest a better prognosis as a marker for acute coronary thrombosis that can be intervened upon[7]. However, the prognostic value of the post-resuscitation ECG has not been thoroughly assessed in ACS presenting with OHCA, and few studies have included patients with a broad spectrum of ACS and OHCA. Accordingly, we sought to characterize electrocardiographic findings on the presenting and follow-up ECGs in patients with ACS and OHCA who survived to hospital admission.

## METHODS

The Global Registry of Acute Coronary Events (GRACE) and Canadian Acute Coronary Syndrome Registry I (ACSI) were multinational, prospective, observational studies of patients with the entire spectrum of ACS[8-10]. The present study was based on the cohort of patients who participated in the ECG substudy of GRACE and ACSI[11]. The GRACE ECG substudy enrolled 7786 patients from 94 sites in 14 countries between March 1999 and January 2004. Patients included were those age ≥18 who were admitted to hospital for presumptive ACS with at least one of: ischemic ECG changes, elevated cardiac biomarkers, or a history of documented coronary artery disease. ACSI enrolled 4364 patients from 51 sites in 9 provinces in Canada between September 1999 and June 2001. Patients included were those age ≥18 who were admitted to hospital within 24 hours of symptoms suggesting acute cardiac ischemia. Consecutive enrollment was encouraged and patients who died before hospital admission were excluded from both registries. Those with an ACS precipitated by a concurrent medical, surgical or traumatic event were also excluded from either registry. Patients with incomplete ECG data were excluded from the present analysis (n=110). In total, 12,040 patients formed the final study cohort.

Standardized case report forms were used to collect data on patient demographics, baseline clinical characteristics, in-hospital management and outcomes. Follow-up was performed by telephone to determine vital status and the incidence of recurrent cardiovascular events. Study protocols were approved by local review boards and participants provided informed consent when required.

All patients had ECGs recorded at the time of admission and at 24-48 hours after presentation, regardless of in-hospital interventions. ECGs were sent to the core laboratory at the Canadian Heart Research Centre for interpretation by trained physicians who were blinded to clinical and outcome data. The core laboratory had prior experience in the systematic evaluation of ECGs with excellent inter-observer and intra-observer agreement (93-99% and 100%, respectively)[11-13]. The presence of ST-segment elevation, ST-segment depression, T wave inversion, Q waves, left bundle branch block (LBBB) and right bundle branch block (RBBB) were recorded on the ECG according to standard definitions. The sum, and total number of leads with ST-segment deviation were also recorded. The primary outcome of this study was the frequency of presenting ECG findings according to OHCA on presentation. Secondary outcomes included in-hospital and cumulative 6-month mortality.

Categorical data are presented as percentages and continuous variables as medians with interquartile ranges (IQR). Patients were grouped according to presentation with OHCA. We examined for differences between groups using the Pearson chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables. Among ACS patients with OHCA, we determined the association between ST-segment deviation and bundle branch blocks with in-hospital and 6-month mortality. Heterogeneity testing was performed using the Breslow-Day test. The McNemar test was used to compare the findings of the presenting ECG and follow-up ECG. Analysis was performed using SPSS (version 22, IBM) and statistical significance was set at a 2-sided p value <0.05.

## RESULTS

Baseline characteristics of 12,040 ACS patients who survived to hospital admission are displayed in Table 1, grouped by the presence of OHCA. Patient groups are outlined in Figure 1. In total, 215 (1.8%) of ACS patients presented to hospital after a resuscitated OHCA; they were more likely to be current smokers and less likely to have a history of dyslipidemia, angina, prior PCI or coronary bypass surgery. They more frequently had higher Killip class, GRACE risk scores and worse left ventricular ejection fraction. Characteristics among OHCA patients according to ST-segment elevation and LBBB are provided in Supplementary Tables 1 and 2.

On the presenting ECG, patients with OHCA had significantly higher rates of ST-segment elevation, ST-segment depression, T wave inversion, precordial Q waves, LBBB and RBBB as compared to those without OHCA (Table 2). Patients with OHCA had a greater number of leads with ST-segment elevation and ST-segment depression, as compared to those patients without. The magnitude of ST-segment elevation and depression was also greater in the OHCA group (Table 3). Table 4 describes in-hospital management according to cardiac arrest upon presentation. Among patients with OHCA, the use of cardiac catheterization or in-hospital PCI was not associated with ST-segment elevation, ST-segment depression, LBBB or RBBB. There was a higher risk of in-hospital CABG among patients with ST-segment depression as compared to those without (5.1% vs. 0.0%, p=0.049).

Compared to patients without OHCA, the group with OHCA had significantly higher rates of in-hospital mortality, heart failure and sustained ventricular fibrillation as well as higher cumulative 6-month mortality (Table 5). Among patients with OHCA, those with ST-segment elevation had a significantly lower in-hospital mortality (21% vs. 33%, p=0.044) and a trend towards lower 6-month mortality (27% vs. 39%, p=0.060) compared to those without ST-segment elevation. Conversely, among patients with OHCA, LBBB was associated with significantly higher in-hospital and 6-month mortality rates (58% vs. 22%, p<0.001 and 65% vs. 28%, p<0.001 respectively), while ST-segment depression and RBBB were not associated with either (Figure 2). Among patients with OHCA in GRACE only (n=7769), there was no association between the presence of ST-segment elevation in aVR with in-hospital mortality (50% vs. 31%, p=0.16). However, ST-segment elevation in aVR was associated with a significantly higher cumulative 6-month mortality (64% vs. 37%, p=0.048).

With regard to heterogeneity testing, RBBB was not associated with in-hospital mortality in either group (Breslow-Day p=0.61). LBBB was associated with a greater increase in in-hospital mortality in the OHCA group (Breslow-Day p=0.049; p<0.001 for both). ST-segment elevation was associated with lower in-hospital mortality in OHCA patients but higher in-hospital mortality in non-OHCA patients (Breslow-Day p=0.003; p=0.044 and p<0.001 respectively).

RBBB was not associated with 6-month mortality in either group (Breslow-Day p=0.41). LBBB was uniformly associated with higher 6-month mortality in those with and without OHCA (Breslow-Day p=0.19, p<0.001 for both). ST-segment elevation was associated with lower 6-month mortality in OHCA patients but higher 6-month mortality in non-OHCA patients (Breslow-Day p=0.02; p=0.06 and p=0.038 respectively).

Among 208 patients who survived to the 24-48 hour follow-up ECG, those with OHCA had higher rates of LBBB and precordial Q waves, but not RBBB, as compared to those without (Table 6). Overall, among those patients with OHCA, the frequencies of LBBB and RBBB were lower on the 24-48 hour follow-up ECG as compared to the presenting ECG (7.2% vs. 13%, p=0.019 and 3.8% vs. 11%, p=0.001, respectively). In total, 63% of bundle branch blocks (either RBBB or LBBB) on the presenting ECG were transient, and had resolved by 24-48 hours.

**DISCUSSION**

In this ECG core laboratory substudy of over 12,000 patients with ACS who survived to hospital admission, those with OHCA had higher initial rates of ST-segment elevation, LBBB and RBBB, as compared to ACS patients without. Among those with OHCA, ST-segment elevation was associated with lower in-hospital mortality, while LBBB was associated with higher in-hospital and 6-month mortality. RBBB was not associated with either in-hospital or 6-month mortality.

Post–cardiac arrest ECG changes are frequent and less specific for ACS than in the non-OHCA setting[14]. This may be secondary to metabolic and electrophysiological impact of the cardiac arrest itself or to the brain-heart connection[15]. Therapeutic hypothermia also has an impact on electrocardiographic findings[16, 17]. Nevertheless, there is general agreement that patients resuscitated from OHCA with ST-segment elevation should undergo emergent coronary angiography[1-5].

Outcomes of resuscitated patients after ischemic OHCA are poor and prognostication is challenging[6, 18, 19], though presenting clinical features, quality of resuscitation and neurologic assessment can help predict in-hospital and long term mortality[20-23]. Given the complex, multisystem nature of post-resuscitation care, we recognize that ECG findings may provide prognostic insights into only one aspect of recovery. Nevertheless, the prognostic value of the presenting ECG has not been well studied, and it is possible that it may predict cardiac outcomes in addition to guiding early invasive management.

Pleskot et al demonstrated higher long-term survival rates among 149 patients hospitalized with STEMI in the setting of OHCA as compared to patients without STEMI[7], but there are limited data replicating this finding[24]. Our results support the notion that ST-segment elevation is associated with improved outcomes in patients with ACS and OHCA. This may reflect earlier recognition of an ischemic etiology for cardiac arrest, and an infarct related arterial occlusion that can be treated medically or interventionally. Indeed, in our analysis, patients with OHCA received more fibrinolytic therapy and had a shorter median time to cardiac catheterization from hospital arrival. However, they did not have higher overall rates of cardiac catheterization or PCI as compared to patients without OHCA. Moreover, among those with OHCA, ST-segment elevation was not associated with increased rates of cardiac catheterization. This likely reflects a generally less aggressive catheterization strategy in ACS management over a decade ago; at the time of data collection, fibrinolysis was the mainstay of reperfusion therapy. The majority of patients were not considered for primary PCI, although, it is also possible that higher risk ACS patients were paradoxically managed more conservatively.

With respect to bundle branch blocks, previous studies in the general population have demonstrated that presenting RBBB, but not LBBB, is independently associated with worse outcomes following ACS[25, 26]. Grand et al, in a substudy of the Targeted Temperature Management Trial, found that RBBB but not LBBB, was associated with significantly higher 6-month mortality in the unadjusted model only. They also observed that the majority of bundle branch blocks (92%) had resolved 4 hours after admission[27]. While the prevalence of bundle branch blocks in this study (22%) is similar to that previously reported (21-24%)[16, 27], the presence of LBBB was strongly associated with worse short- and long-term outcomes, while RBBB was not. This may relate to patient selection as we only studied patients with OHCA in the setting of ACS. Our cohort also had a lower rate of transient bundle branch block as compared to Grand et al (63% vs 92%)[27] which might imply that fewer patients had temporary ischemia to the conduction system or a higher prevalence of pre-existing bundle branch blocks.

Importantly, LBBB and Q waves have potential confounders that must be considered. In the setting of ACS, they can indicate acute cardiac injury from active ischemia, but also may represent pre-existing and more severe underlying coronary artery disease, structural heart disease and left ventricular dysfunction[26, 28]. These might in part contribute to the worse outcomes associated with LBBB and were not accounted for in this study. Nevertheless, the association between LBBB with in-hospital mortality is striking, and this remained true at 6 months. There was also less heterogeneity observed with respect to bundle branch blocks and outcomes as compared to ST-segment changes.

We believe the findings of this study are relevant to current clinical practice, but we recognize that the results may be different from real world data of today, where primary PCI is more readily available and targeted temperature management is standard of care. However, our primary objective was to assess presenting ECG findings, which should not be influenced by contemporary in-hospital management. Moreover, outcome and follow-up ECG analysis were purposefully limited in light of the aforementioned limitations. Understanding this, our study is hypothesis generating and suggests that the presenting ECG should be re-considered as a readily available and easy to interpret tool that may help predict cardiac outcomes after guiding early invasive management.

Our study has important strengths. We studied a large, prospective, multinational, registry cohort that included the entire spectrum of ACS and only ischemic OHCA. A validated core laboratory independently assessed all ECGs, thereby enhancing the internal validity of the results[12, 13]. Our clinical endpoints focused on vital status, and 6-month mortality data were available for majority of patients. Heterogeneity in the relationship between ECG findings and outcomes was assessed.

We also acknowledge several study limitations. First, patients who died before admission were not included. Second, given the relatively small number of patients with OHCA, there was inadequate power to assess the independent prognostic value of ECG findings. We did not account for ST-segment elevation caused by cardiac contusion during CPR[29, 30], nor LBBB associated with myocardial dysfunction, heart failure and cardiac comorbidities[26, 28]. Third, we lacked data to calculate QRS score for myocardial infarction size and we did not record post-arrest ICD implantation. Fourth, historical ECGs were not available and it is therefore unknown which ECG findings were present prior to OHCA. Lastly, as previously discussed, we utilized data from more than a decade ago.

In conclusion, compared to ACS patients without cardiac arrest, those with OHCA who survived to hospital admission had higher rates of ST-segment elevation, ST-segment depression, T-wave inversion, precordial Q waves, LBBB and RBBB. Among ACS patients with OHCA, ST-segment elevation was associated with a lower in-hospital mortality, while LBBB was associated with higher in-hospital and 6-month mortality. These findings suggest that the presenting ECG features may be valuable in predicting cardiac outcomes, in addition to guiding initial cardiac management. Further research is required using a more contemporary patient cohort.

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## FIGURE LEGENDS

Figure 1. STROBE flow diagram of the study population

Figure 2. In-hospital and 6-month mortality among patients with OHCA according to ECG finding

Table 1. Baseline patient characteristics according to cardiac arrest upon presentation

| Variable | Cardiac Arrest No (n=11825) | Cardiac Arrest Yes (n=215) | p-value |
|---|---|---|---|
| Age (years)* | 66 (56, 75) | 64 (55, 74) | 0.25 |
| Gender female | 33% | 31% | 0.52 |
| Current smoker | 29% | 38% | 0.006 |
| Diabetes mellitus | 24% | 24% | 0.94 |
| Hypertension | 55% | 50% | 0.12 |
| Dyslipidemia | 46% | 33% | <0.001 |
| Prior angina pectoris | 57% | 40% | <0.001 |
| Prior myocardial infarction | 32% | 28% | 0.19 |
| Prior heart failure | 11% | 9.9% | 0.69 |
| Prior transient ischemia attack or stroke | 7.9% | 8.0% | 0.99 |
| Prior percutaneous coronary intervention | 15% | 8.0% | 0.004 |
| Prior coronary bypass | 12% | 7.5% | 0.039 |
| Systolic blood pressure (mmHg)* | 142 (124, 162) | 123 (101, 144) | <0.001 |
| Diastolic blood pressure (mmHg)* | 80 (70, 91) | 72 (60, 90) | <0.001 |
| Heart rate (bpm)* | 75 (64, 89) | 88 (70, 110) | <0.001 |
| Killip class | | | |
| I | 82% | 64% | <0.001 |
| II | 15% | 15% | |
| III | 3.4% | 10% | |
| IV | 0.5% | 11% | |
| Serum creatinine (µmol/L)* | 90 (79, 108) | 102 (85, 123) | <0.001 |
| Initial cardiac biomarker(s) elevated** | 42.0% | 45% | 0.40 |
| GRACE risk score** | 128 (105, 154) | 191 (163, 227) | <0.001 |

*Median (25th, 75th percentile)
**Cardiac biomarkers included creatine kinase (CK), creatine kinase-myocardial band (CK-MB), or troponin depending on the local site, based on its upper limit of normal

Table 2. Presenting ECG findings according to cardiac arrest upon presentation

| Presenting ECG findings (excluding aVR) | Cardiac Arrest | | p-value |
|---|---|---|---|
| | No (n=11825) | Yes (n=215) | |
| Complete left bundle branch block | 4.5% | 12% | <0.001 |
| Complete right bundle branch block | 4.7% | 10% | <0.001 |
| Any ST deviation ≥0.5mm | 75% | 82% | 0.014 |
| ST elevation ≥1.0mm in ≥ 2 contiguous leads | 32% | 54% | <0.001 |
| ST depression ≥0.5mm in any lead | 51% | 65% | <0.001 |
| T wave inversion in ≥2 contiguous leads | 27% | 21% | 0.047 |
| Q wave in ≥2 precordial leads | 14% | 21% | 0.004 |
| Q wave in I and aVL | 3.3% | 2.3% | 0.44 |
| Q wave in II and aVF | 4.6% | 4.2% | 0.78 |

Table 3. Quantitative presenting ECG findings according to cardiac arrest upon presentation

| Presenting ECG findings (excluding aVR) | Cardiac Arrest | | p-value |
|---|---|---|---|
| | No (n=11825) | Yes (n=215) | |
| Sum of ST elevation ≥1.0mm in all leads | 0 (0, 3) | 2 (0, 9.5) | <0.001 |
| Number of leads with ST elevation ≥1mm | 0 (0, 2) | 2 (0, 4) | <0.001 |
| Sum of ST depression ≥0.5mm in all leads* | -0.5 (-2.5, 0) | -2 (-6, 0) | <0.001 |
| Number of leads with ST depression ≥0.5mm | 1 (0, 3) | 2 (0, 4) | <0.001 |

Data expressed as median (25th, 75th percentile)
*Magnitude of ST depression expressed as negative

Table 4. In-hospital management, angiographic findings and left ventricular systolic function according to cardiac arrest upon presentation

| Variable | Cardiac Arrest | | p-value |
|---|---|---|---|
| | No (n=11825) | Yes (n=215) | |
| Left ventricular function* | | | |
| Normal | 54% | 36% | <0.001 |
| Mildly impaired | 24% | 24% | |
| Moderately impaired | 19% | 32% | |
| Severely impaired | 2.6% | 8.4% | |
| In-hospital management | | | |
| Fibrinolytic therapy | 18% | 41% | <0.001 |
| Intravenous inotropes in first 24 hours** | 3.9% | 40% | <0.001 |
| Intravenous nitrates in first 24 hours** | 44% | 29% | 0.001 |
| Amiodarone in first 24 hours** | 4.1% | 39% | <0.001 |
| Cardiac catheterization | 50% | 47% | 0.27 |
| Median time to cardiac catheterization (d)^ | 3 (1,6) | 1 (0,4) | 0.001 |
| Percutaneous coronary intervention | 26% | 29% | 0.34 |

| | | | |
|---|---|---|---|
| Coronary bypass surgery | 3.8% | 3.3% | 0.69 |
| Coronary angiographic narrowing*** | | | |
| ≥50% left anterior descending | 65% | 69% | 0.43 |
| ≥50% left circumflex | 50% | 56% | 0.29 |
| ≥50% right coronary | 58% | 59% | 0.92 |
| Triple vessel or left main | 30% | 31% | 0.94 |
| Discharge medications (hospital survivors only) | | | |
| Aspirin | 89% | 87% | 0.45 |
| Oral anticoagulant | 7.6% | 16% | <0.001 |
| Beta blocker | 77% | 76% | 0.89 |
| ACE inhibitor / angiotensin receptor blocker | 62% | 71% | 0.024 |
| Lipid lowering agent | 63% | 62% | 0.88 |
| Amiodarone^^ | 4.6% | 12% | 0.001 |

*Data available for n=7175 who had LVEF assessment in hospital
**Data available for n=7684 in GRACE only
*** Data available for n=4348 who had cardiac catheterization in hospital; patients with previous coronary bypass surgery were excluded from angiographic analysis
^Median (25th, 75th percentile)
^^Data available for n=6712 in GRACE only

Table 5. Clinical outcomes in-hospital and at 6 months follow-up according to cardiac arrest upon presentation

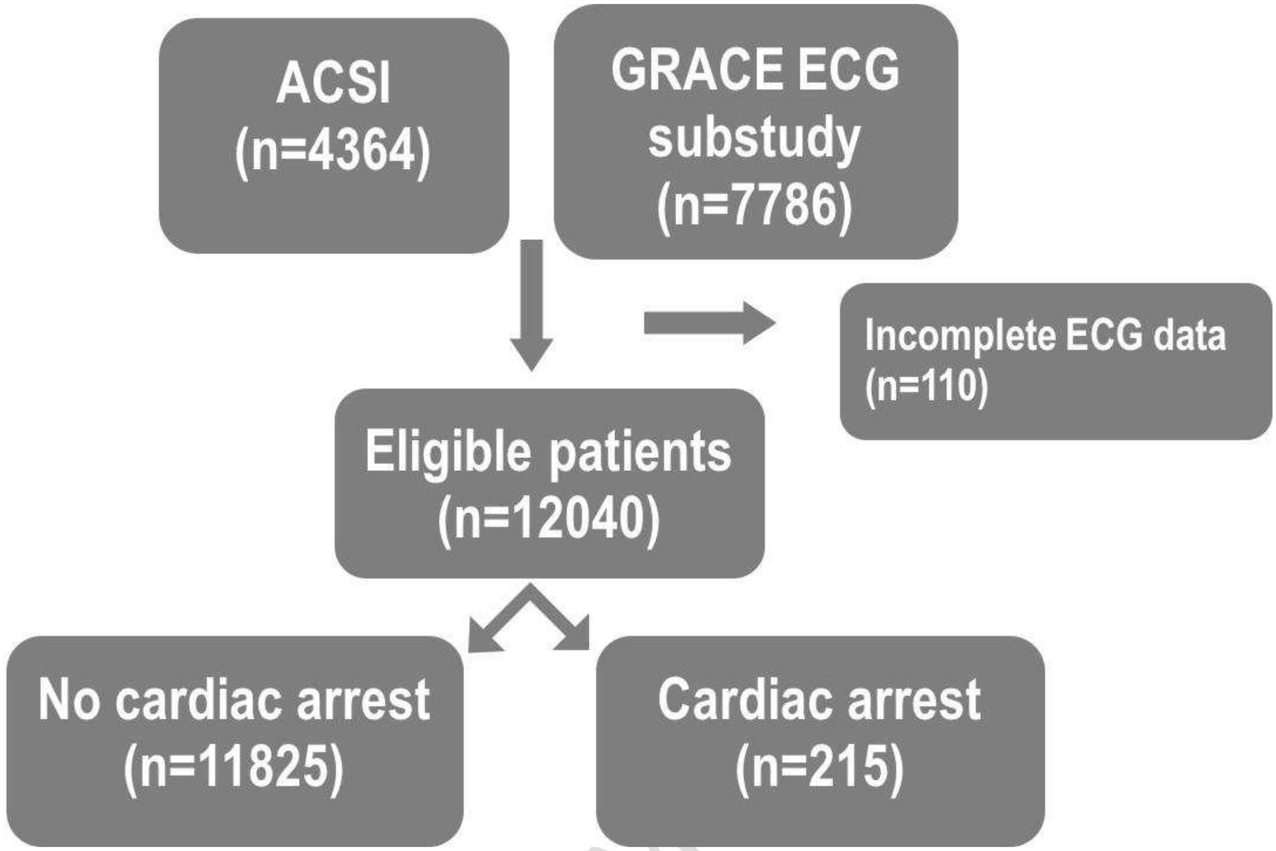
| Clinical outcome | Cardiac Arrest | | p-value |
|---|---|---|---|
| | No (n=11825) | Yes (n=215) | |
| In-hospital outcomes | | | |
| Death | 3.9% | 27% | <0.001 |
| Myocardial re-infarction | 8.0% | 11% | 0.084 |
| Heart failure* | 15% | 30% | <0.001 |
| Cardiac arrest/ ventricular fibrillation** | 4.2% | 34% | <0.001 |
| 6-month outcomes | | | |
| Cumulative mortality*** | 8.1% | 33% | <0.001 |

*Data available for n=7698
**Data available for n=7704
***Data available for n=10715

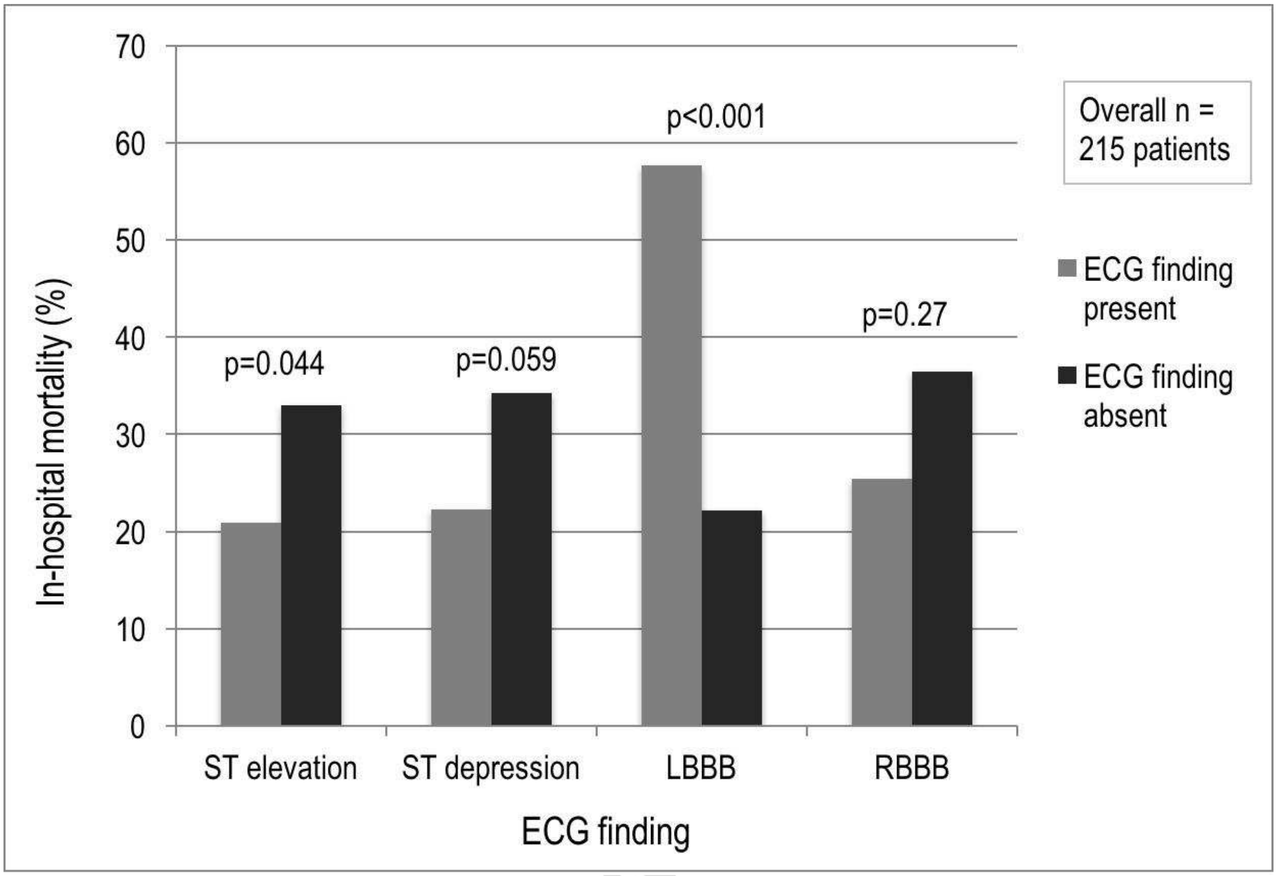
Table 6. 24-48 hour follow-up ECG findings according to cardiac arrest upon presentation

| Presenting ECG findings | Cardiac Arrest | | p-value |
|---|---|---|---|
| | No (n=11825) | No (n=11825) | |
| Complete left bundle branch block | 3.9% | 7.2% | 0.016 |
| Complete right bundle branch block | 4.5% | 3.8% | 0.64 |
| Q waves in ≥2 precordial leads | 14% | 24% | <0.001 |
| Q waves in I and aVL | 8.4% | 10% | 0.37 |

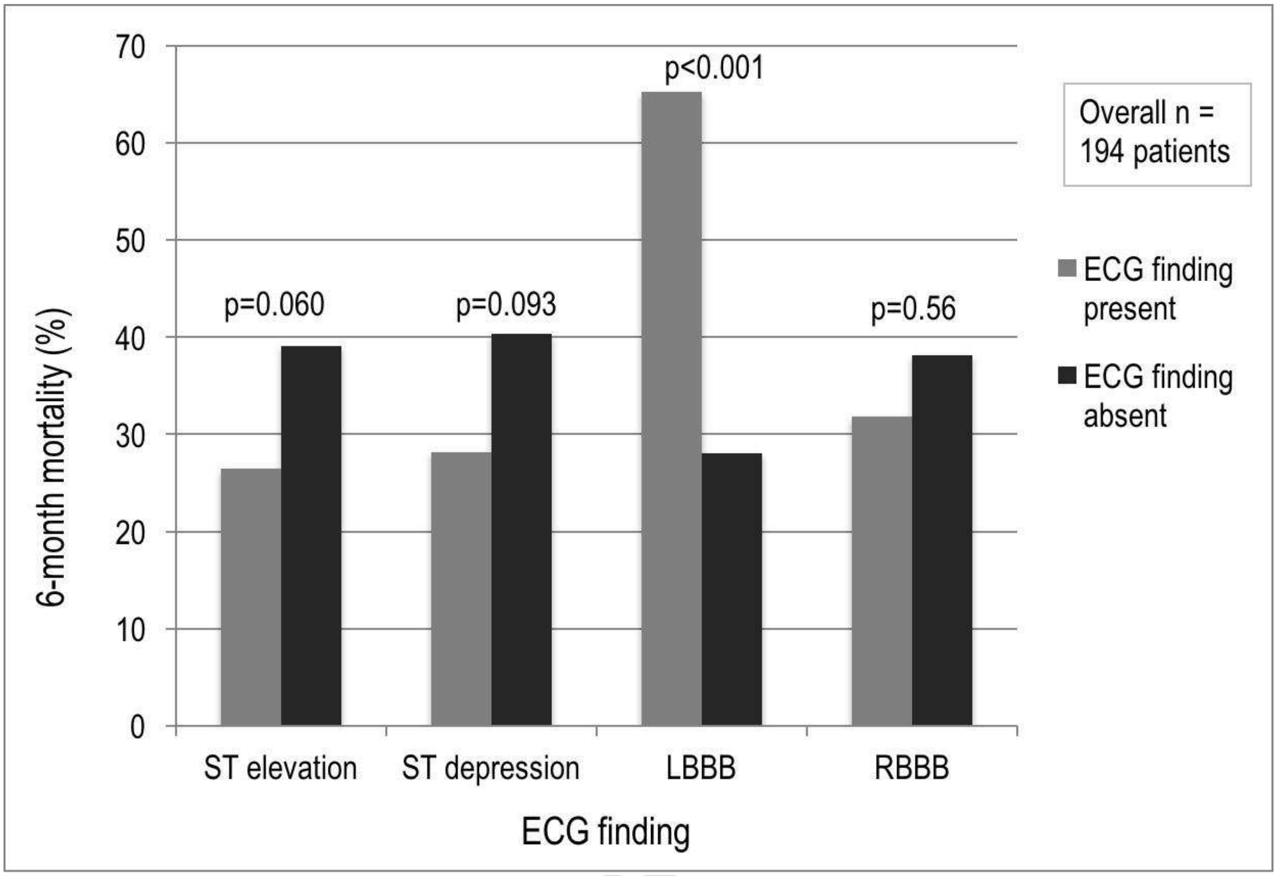
| | | | |
|---|---|---|---|
| Q waves in II and aVF | 21% | 23% | 0.46 |




OHCA_ECG_GRACE_figure1_AJC.jpg




OHCA_ECG_GRACE_figure2a_AJC.jpg




OHCA_ECG_GRACE_figure2b_AJC.jpg