# A Cohort Study of Risk Factors and Clinical Outcome Predictors for Patients Presenting With Unstable Angina and Non ST Segment Elevation Myorardial Infraction Undergoing Coronary Intervention

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**SUMMARY**

**Introduction: Thrombolysis in Myocardial Infarction (TIMI) score has been used to predict outcomes in patients presenting with unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI). Our study assessed other clinical predictors for patients with UA/NSTEMI undergoing early percutaneous coronary intervention (PCI).**

**Materials and Methods: A cohort of 3822 patients presented with UA/ NSTEMI from June 2001 to March 2008 in our center were recruited. Patients underwent PCI during admission. We analyzed the potential risk predictors for major adverse cardiac events (MACE) and death at 1 month and 6 month.**

**Results: Median age was 57.1±11.1, 78.1 percent men, 34.5 percent had diabetes, 58.8 percent had hypertension. Coronary lesions involving left main and proximal left anterior descending artery was 27.6 percent. 36.1 percent had NSTEMI. Significant predictors for mortality at 6 months were age older than 70 years (p=0.001, OR = 5.5), female gender (p=0.001, OR=2.98), anaemia (p<0.001 OR=8.47), baseline renal impairment (P<0.001, OR=7.38) and development of contrast nephropathy (CIN) which was defined as 25% or 0.5 mg/dl increase from baseline Creatinine within 48 h after PCI (p=0.005, OR=5.8). Diabetes was a predictor of MACE at 6 months (p=0.003, OR=1.51) but not mortality.**

**Conclusions: In patients with UA/NSTEMI, our study showed that MACE and mortality were increased in elderly, female and presence of anaemia. Mortality, but not MACE was increased in chronic renal impairment and development of CIN; while diabetes increased only MACE, but not mortality.**

**Summary: We analyzed a cohort of 3822 patients with UA/NSTEMI underwent PCI and found that elderly, female, presence of anemia, diabetes and chronic renal impairment were high risk predictors for adverse clinical outcome. In addition, development of CIN increased mortality.**

**KEY WORDS:**
*NSTEMI, Unstable angina*

## INTRODUCTION

The Thrombolysis in Myocardial Infarction (TIMI) score has been developed to predict short term clinical outcomes in patients presenting with unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI)[1]. The TIMI score include old age, presence of cardiac risk factors including family history, diabetes, hypertension, hyperlipidmeia and smoking, history of coronary stenosis, previous aspirin use, severe recent onset angina, abnormal ECG ST segment and rise in cardiac markers[2].

TIMI score was developed in the last decade and many of the study patients receive intravenous thrombolytics instead of percutaneous coronary intervention (PCI). Hence, the TIMI score may be less applicable in current era when most patients undergo early coronary angioplasty.

In this study, we aim to assess the additional clinical predictors for morbidity and mortality in UA/NSTEMI patients undergoing PCI.

## MATERIALS AND METHODS

The study was conducted in a University cardiac center. The study design was a retrospective cohort study using the cardiology database in the cardiac center. The cardiology database was a specially designed template used to document and store patient's clinical and procedural data. Data of consecutive patients undergoing coronary angiogram and PCI was recorded in prospective manner by interventional cardiologists and cardiac catheterisation lab fellows. Follow up of the clinical outcomes post PCI was performed by a dedicated team of research nurses during clinical visits and via telephone interviews. The database was maintained by a dedicated team of computer technologists. Various data involving patient clinical characteristics such as hypertension, diabetes, smoking status and family history; blood tests results including cardiac enzymes, renal panel and full blood counts; PCI parameters and clinical outcomes were documented in the pre-specified data columns. Data extraction was authorized and approved by cardiac department and institutional ethic committee.

Our study cohort consisted of 3822 consecutive patients extracted from the cardiology database presented with UA/NSTEMI and underwent PCI between June 2001 and March 2008. PCI were performed as inpatient procedures. The mean duration of hospital stay was 3.8±2.8 days. The mean timing of PCI from the initial admission was 1.8±1.5 days.

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76.6% of patient underwent PCI within 48hours of admission. 89.2% of patients underwent PCI within 72 hours of admission. We analyzed the various potential risk factors for prediction of major adverse cardiac events (MACE) and death at 1 month and 6 months. MACE is defined as a composite clinical end point of death, non-fatal myocardial infarction and target vessel revascularization.

PCI was performed according to standard clinical practice. The cardiology unit offered 24 hour and 7 days PCI service. Angioplasty technique and use of adjunctive pharmacologic therapies were left to the discretion of the interventional cardiologists. Unless contraindicated due to drug allergy, all patients received loading doses of 300 mg of aspirin and 300mg of clopidogrel before the procedure and followed by 100mg aspirin and 75mg clopidogrel daily. Duration of use dual antiplatelets regime used was according to the concurrent guidelines [3].

Inclusion criteria included all patients underwent PCI and had database coding for UA/NSTEMI. Patients must undergo coronary angiogram and culprit lesion PCI during the same admission.

Exclusion criteria included patients presented with UA/NSTEMI who had severe left main and / or multi vessel disease which was not amendable to PCI and / or patients who were referred for bypass operation. Patients who had STEMI or evolved AMI were excluded. Patients received intravenous thrombolytics for acute MI were excluded.

*Clinical definitions and follow-up.*
UA is defined as ischemic discomfort that occurs at rest or with minimal exertion, occurs in a crescendo pattern, or is severe and of new onset[4]. If these symptoms are accompanied by a release of cardiac biomarkers of necrosis e.g. creatine kinase-MB isoenzyme (CK-MB) or cardiac troponin, then a NSTEMI is said to have occurred[5].

Baseline blood sample was taken before PCI. CIN was defined as 25% or 0.5 mg/dl increase from baseline Creatinine (Cr) within 48 h after PCI[6]. The highest post-procedural Cr at 24-48 hours was used for the calculation.

Anaemia was defined as baseline serum hemoglobin (Hb) < 11g/dl.

Renal Impairment was defined as baseline eGFR <60 ml/min/1.73m$^2$ using MDRD formula[7].

Hypotension was defined as systolic blood pressure <100 mmHg by aortic opening pressure during coronary angiogram.

Cardiogenic shock was defined as sustained hypotension for greater than 30 min with clinical evidence of tissue hypoxia[8]. Prespecified clinical, laboratory and demographic information were obtained from case notes by independent research nurses who were unaware of the objectives of the study.

*Statistical analysis.*
Continuous data were reported as mean value ± SD, unless otherwise specified. Categorical data were presented as absolute values and percentages. Comparison of continuous variables was performed by Student t test. Chi-square and Fisher exact tests were performed for comparison of categorical variables as appropriate. Multivariate analysis with an enter model including variables of age, gender, renal impairment, diabetes mellitus, hypertension, anemia, creatinine kinase level, contrast nephropathy, left ventricular ejection fraction (LVEF) and cardiogenic shock). A p value <0.05 was considered statistically significant. Analysis was conducted using SPSS statistical software (Version 16.0, SPSS Institute Inc., Chicago, Illinois).

Potential risk predictor variables were selected from baseline characteristics that could be readily identified at presentation. The list was further restricted to include only those characteristics be important variables in predicting outcome.

## RESULTS

Baseline demographics are shown in Table I. Mean age was 57 years, 78% men, 34% had diabetes, 58% had hypertension and 52% were active smokers. Baseline anaemia was present in 6.5% and renal impairment in 7.3% of the cohort. Coronary lesions involving left main (LM) was 0.9% and proximal left anterior descending artery (LAD) was 27.6%. Patients who had LM disease also had concurrent proximal LAD disease. 36.1% had NSTEMI. 63.9% was labeled as UA. Among the UA patient who had abnormal ECG pattern including abnormal ST segment depression and abnormal T wave were 56.2% and 48.8% respectively. Mean left ventricular ejection fraction (LVEF) was 48.0 ± 18.6%. The LVEF was assessed by trans-thoracic echocardiogram within 4 months of procedure.

The most significant clinical predictors for mortality and MACE are listed in table II. The odd ratio and p value was derived after multivariate analysis taken into account of age, gender, diabetes, hypertension, hyperlipidemia, smoking, renal impairment, anemia, contrast nephropathy, cardiogenic shock, creatinine kinase level, LVEF and stents characteristics as listed in Table I.

**Table I: Baseline Demographics**

| Demographics | Percentage |
|---|---|
| Age (years) | 57.1±11.1 |
| Gender / Male | 78.1% |
| Hypertension | 58.8% |
| Diabetes | 34.5% |
| Hyperlipidemia | 76.3% |
| Smoking | 52.5% |
| Anemia (Hb < 11g/dL) | 6.5% |
| Family history of IHD | 10.8% |
| Chronic Renal Impairment | 7.3% |
| UA 63.9% | |
| NSTEMI | 36.1% |
| Cardiogenic Shock | 4.4% |
| Number of Stents | |
| 1 | 76.2% |
| 2 | 8.5% |
| ≥3 | 1.3% |
| Stent length mm | 25.2 ±7.0 |
| LM & proximal LAD | 27.6% |
| Creatinine Kinase (U/L) Level | 108 (100-4126) |
| Development of Contrast Induced Nephropathy (CIN) | 8.4% |
| LVEF (%) | 48.27±12.70 |

**Table II: Adjusted Significant Predictors of MACE and Mortality.**

| Significant Clinical Predictors | Death at 1 month | Death at 1 month | Death at 6 months | Death at 6 months | MACE at 1 month | MACE at 1 month | MACE at 6 months | MACE at 6 months |
|---|---|---|---|---|---|---|---|---|
| | Odds Ratio | P Value | Odds Ratio | P Value | Odds Ratio | P Value | Odds Ratio | P Value |
| Age (>70years) | 2.03 (0.47-8.79) | 0.279 | 5.5 (2.32-12.99) | 0.001 | 2.21 (1.09-4.51) | 0.042 | 1.69 (1.0-2.87) | 0.049 |
| Gender (Female) | 2.49 (1.06-5.85) | 0.031 | 2.98 (1.49-5.95) | 0.001 | 1.93 (1.25-2.98) | 0.001 | 1.93 (1.22-2.19) | 0.001 |
| Diabetes | 1.89 (0.81-4.37) | 0.131 | 1.79 (0.90-3.56) | 0.095 | 2.20 (1.46-3.32) | <0.001 | 1.51 (1.15-1.97) | 0.003 |
| Anemia (Hb < 11g/dL) | 3.86 (1.06-14.08) | 0.027 | 8.47 (3.66-19.61) | <0.001 | 2.40 (1.24-4.67) | 0.007 | 2.03 (1.26-3.26) | 0.003 |
| Baseline Renal Impairment | 6.0 (1.83-19.75) | 0.001 | 7.38 (2.91-18.68) | <0.001 | 1.75 (0.82-3.74) | 0.149 | 1.54 (0.91-2.61) | 0.108 |
| Development of Contrast Nephropathy | 7.37 (1.74-31.29) | 0.019 | 5.80 (1.94-17.36) | 0.019 | 5.80 (0.99-5.97) | 0.050 | 1.67 (0.88-3.18) | 0.116 |

Old age of greater than 70 years was an important predictor for MACE and mortality at 6 months. Female patients had higher MACE and mortality at 6 months comparing to male patients. Presence of diabetes increased risk for MACE at 1 and 6 months. There was a trend towards higher mortality in diabetic patients; however this did not reach statistical significant values. Anemia with hemoglobin less than 11g/dl had adverse impact on the survival and MACE rates. Baseline renal impairment and development of contrast nephropathy post PCI increased mortality. The type of stents used including bare metal stents and drug eluting stents used did not have significant impact on mortality.

## DISCUSSION

This is a retrospective cohort study involving large number of patients who presented with acute coronary syndrome comprising of UA/NSTEMI undergoing PCI in a single cardiac center. The aim of the study was to assess the impact of risk factors which were not routinely used in the TIMI validation score on the short term clinical outcome. We paid attention to risk factors including gender, anaemia, renal impairment, development of contrast nephropathy and type of stents used.

The study end points were clinically driven which include mortality and MACE at 1 and 6 months.

According to the TIMI (UA/NSTEMI) score, old age (≥65) and presence of three of more risk factors namely diabetes, hypertension, hyperlipidemia, smoking and family history of ischemic heart disease increased MACE and mortality. In our study, hypertension, hyperlipidemia, smoking and family history were not significant independent predictors of MACE and mortality in short term. Diabetes increased MACE (OR=1.51, p=0.003 at 6 months) and showed a trend toward increased mortality but not reaching a statistically significant p value. The main underlying reason of higher MACE was driven by increased incidence of target vessel revascularisation. This suggests that among the traditional risk factors, presence of diabetes is the most predictive factor for adverse clinical event. As diabetic patients are known to have a greater subsequent need for revascularization, PCI in the setting of diabetes should hence use drug eluting stents instead of bare metal stent to reduce rate of in stent restenosis and subsequent PCI. In addition, diabetics should be considered CABG when multiple significant coronary lesions are detected and the left ventricular systolic function is impaired[9].

The more important risk predictors for MACE and mortality in our study were presence of anaemia and baseline renal impairment (GFR<60). The presence of anaemia was a very strong predictor for death (OR=8.4, p<0.001 at 6 months) and MACE (OR=2.0, p=0.003 at 6 months). Anaemia has been shown to be a predictor for death in AMI patients in previous study[10]. Compared to patients who did not have anaemia, patient who have anemia were more likely to be older and more frequently female. There was higher prevalence of cardiovascular risk factors including renal impairment. After adjustment for potential confounders in our study, anemia remained as a significant predictor for MACE and mortality at short term post PCI. Blood transfusion which required post PCI has also been independently linked to further increase risk of adverse events. This may partly caused by higher likelihood of congestive heart failure post transfusion[11].

Baseline renal dysfunction and development of CIN were important predictors of MACE and mortality. Patients with renal impairment were routinely given saline hydration in our cohort unless contraindicated by fluid overloading status prior to PCI. The standard regime would be saline infusion at a rate of 1ml/kg body weight/hour for 6-12hours before PCI. Patient who developed congestive heart failure at presentation were treated with frusemide and managed according to institutional heart failure pathway. Despite the prophylactic saline hydration to prevent CIN, the adverse clinical outcomes were significant. Hence, it would be prudent to identify these high risk features and consider additional prophylactic therapy including N-acetylcysteine and sodium bicarbonate to prevent the occurrence of CIN[12]. It is worth noting that presence of anemia and renal impairment concurrently had been shown to further increase morbidity and mortality[13].

Female gender has shown to be a significant predictor of MACE and mortality in our cohort after multivariate analysis. Female patients who presented with ACS were more likely to be older and have co-morbid conditions such as a lower body mass, anemia and abnormal eGFR. Females presenting with

AMI has been shown to have higher mortality in previous report[14]. However, a more recent analysis on gender difference in AMI patient taking into account of various confounding factors and adjustment for angiographic disease severity, the 30-day mortality among women was not significantly different than men[15]. Hence more data need to be gathered in future to assess gender as an independent risk for UA/NSTEMI after PCI.

The procedural parameters such as type of stent used (bare metal stents versus drug eluting stents) did not significantly affect the mortality rate at 1 and 6 months. The choice of drug-eluting or bare metal stents was according to angiographic and clinical parameters suggested in guidelines[3]. In general, drug eluting stents were used for longer coronary lesions and smaller coronary vessels. Drug eluting stents were also indicated for diabetic patients. Bare metal stents were used in mostly non-diabetic patients with shorter lesions and vessels with larger reference diameter. Drug eluting stents was avoided in lesions with large thrombotic burden so as to minimize the potential complication of stent thrombosis[16]. The differences in clinical and angiographic risk profile among patients receiving bare and drug eluting stents could explain the equality in clinical outcome.

Our study suggested that among various potential risk factors, old age, female gender, baseline anemia and renal impairment were independently predictive for higher mortality at short term post PCI. Presence of diabetes increased MACE but did not increase mortality after adjusting for other risk factors in the diabetes patients.

## LIMITATIONS

Our study is retrospective in nature and hence the inherent deficiencies during the data analysis. However, the number of subjects studied was large and hence that could still provide reasonable information on the correlation between patient risk profile and clinical outcomes. This was local data and we presented the significant risk predictors during the management of UA/NSTEMI in local population.

## CONCLUSION

In patients presenting with UA/NSTEMI undergoing PCI, old age, female gender, presence of anemia and baseline renal impairment were high risk features. Development of CIN can cause further negative impact on survival at short term. Diabetes increased MACE at short term but did not reach statistical significance for higher mortality. Hence, the presence of such risk predictors should alert the clinician on the high risk presentation.

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