

**Prediction of mortality one year after hospital admission**

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## **Abstract**

**Objective:** Hospital admission, especially for the elderly, can be a seminal event as many patients die within a year. This study reports the prediction of death within a year of admission to hospital of the Simple Clinical Score (SCS) and ECG dispersion mapping (ECG-DM). ECG-DM is a novel technique that analyzes low amplitude ECG oscillations and reports them as the myocardial micro-alternation index (MMI).

**Methods:** a convenient sample of 430 acutely ill medical patients (mean age 67.9 +/- 16.6 years) was followed up for one year after their last admission to hospital.

**Results:** 74 (16.3%) patients died within a year – all but 7 had a SCS  $\geq 5$  and 40% of those with an MMI  $\geq 50\%$  died. Only six of variables were found by logistic regression to be independent predictors of mortality (i.e. age, MMI, Simple Clinical Score, a discharge diagnosis of cancer, hemoglobin below 11 gm%, and prior illness that required the patient to spend more than 50% of daytime in bed). The SCS and MMI plus age were comparable predictors of one year mortality: SCS  $\geq 12$  predicted one year mortality with the highest odds (16.1, Chi square 79.09,  $p < 0.0001$ ) and a score of age plus MMI  $> 104$  had an odds ratio of 9.4 (Chi square 73.50,  $p < 0.0001$ ), identified 69% of deaths, and 43% the 119 patients who exceeded this score were dead within a year.

**Conclusion:** SCS and ECG-DM plus age are clinically useful for long term prognostication. ECG-DM is inexpensive, only takes a few seconds to perform and requires no skill to interpret.

## Introduction

Hospital admission, especially for the elderly, can be a seminal event. It has been reported that more than a quarter of patients over 65 years of age are dead within a year of hospital admission (1). In 2006 we reported the Simple Clinical Score (SCS), a reliable and objective predictor of in-hospital mortality that has been independently validated in several different clinical settings (2-6). Its ability to predict long term prognosis, however, has never been reported.

The five most important components of the SCS are hypotension, hypoxia, hypothermia, inability to stand unaided and ECG abnormality - only four out of 4177 patients with a normal ECG died within 24 hours (7). Performing and interpreting an ECG is time consuming, requires training and skill and can, therefore, be costly and impractical. ECG dispersion mapping (ECG-DM) is a recently developed technology that provides non-invasive assessment of myocardial pathology by analyzing low amplitude oscillations of conventional ECG signals. This method examines not only the tiny fluctuations of the T-wave (T wave alternans) but also micro fluctuations of the P wave and QRS complex. All these micro-deviations are combined into one overall myocardial micro-alternation index (MMI) which is expressed as a percentage (8-10) – if pathological micro-deviations are present throughout the entire myocardium the MMI is 100%, whereas an MMI of 0% indicates a total absence of abnormal micro-deviations.

This study reports the one year follow-up of a previously reported cohort of acutely ill medical patient (11-12) admitted to our hospital. It examines the ability of the SCS and ECG-DM to predict one year mortality compared with the standard 12 lead ECG and other commonly used mortality predictors.

## Methods

All patients were recruited from the unselected acutely ill medical patients admitted to Nenagh Hospital between July 30<sup>th</sup> 2009 and 31<sup>st</sup> March 2010. Of the 1680 patients admitted during this period 455 (27.1%) had the SCS measured and ECG-DM performed on them within 10 to 20 minutes of hospital admission. Since 25 of these patients were readmitted during the study period, this study followed up 430 individual patients (mean age 67.9 SD 16.6 years, range 16 to 99 years) for 365 days after the time of their last admission.

Nenagh Hospital has recently undergone substantial reconfiguration of its service. At the time of this study Nenagh Hospital was small general hospital in rural Ireland serving a population of 60,000. It had a 36 bed acute medical unit with 2,800 admissions per year almost all of which were unplanned emergencies (13). It was served by four consultant physicians each assisted by a team of three physicians in training - each team was on-call every fourth day. The hospital had a five bed ICU capable of cardiac monitoring, external and temporary transvenous pacing, non-invasive and invasive ventilation. Renal dialysis, hematology and oncology units were available at Limerick Regional Hospital, 25 miles away.

The SCS can be quickly performed at the bedside and requires no additional information or investigation other than a 12 lead ECG, ECG-DM (HeartVue system, Medical Computer Systems Ltd., Moscow) is a non-invasive procedure that takes 30 seconds to perform, and only requires the placement of the four standard ECG limb leads. All data was corrected for errors and then entered into an *Epi-Info version 6.0* database (*Center for Disease Control and Prevention, USA*). The ICD10 coded diagnoses recorded at discharge or death were also entered into this database. In particular we examined the ten commonest of 32 co-morbid diagnoses that we have previously reported (13) to have an increased risk of in-hospital mortality (i.e. heart failure, atrial fibrillation, diabetes, hyponatremia, chronic obstructive lung disease, anemia, altered mental status, pneumonia, neoplasia and acute myocardial infarction).

Follow-up was performed by contacting the patient directly and/or their family doctor and/or the hospital's patient administration system for those patients still attending out-patient services. For those patients who had died the exact date of death was obtained from the North Tipperary

Registrar of Births Marriages and Deaths and/or the website rip.ie. No patient was lost to follow-up.

For univariate analysis the continuous variables of age, MMI etc were converted into categorical variables by determining the odds ratio with the highest Chi-squared number for predicting in-hospital mortality. This was done by a process of trial and error. Continuous variables were compared by Student's t test and categorical variables by Chi-square analysis that applied Yates continuity correction – all calculations were performed using *Epi-Info version 6.0 (Center for Disease Control and Prevention, USA)*, and statistical significance was set at a p value <0.05. The independence of variables was tested by logistic regression using Logistic Version 3.11E software (G.E. Dallal, Andover MA) (14). The area under the receiver operating characteristic curves (AUROC) was calculated according to the method of Hanley and McNeil (15).

Ethical approval of the study was obtained from the *Mid-Western Regional Hospital Complex Scientific Research Ethics Committee*, which granted exemption for patient consent.

## Results

Sixteen patients died during their hospital admission (mean length of hospital stay 10.4 SD 7.7 days), and only one patient who died in hospital was under 68 years of age. One year after admission a total of 74 (16.3%) patients had died. The majority of these patients were elderly – one year after admission 69 (23.8%) of the 244 patients over 68 years of age were dead. All but seven of the 74 patients who died during the one year follow-up period had a SCS  $\geq 5$  (Figure 1). Of the seven out of 162 patients with a SCS  $\leq 4$  who died four had cancer, one liver failure and two heart failure with MMI values of 40% and 50%. All of the patients with an MMI below 10% and 90% of those with an MMI between 10 and 20% were still alive one year later, while 40% of those with an MMI  $\geq 50\%$  died (Figure 2).

Apart from breathing rate and oxygen saturation there were no differences in the vital signs on admission of the patients who died. Although patients who died had a higher white cell count and urea and lower hemoglobin levels, their admission sodium and potassium levels were similar to those of survivors. However, numerous categorical variables identified patients who more likely to die within a year (Table 1), those with highest Chi-square number were: Simple Clinical Score  $\geq 12$ , age combined with MMI  $> 104$ , prior illness that required the patient to spend more than 50% of daytime in bed, age  $> 68$  years, being unable to stand without help, a discharge diagnosis of cancer, and an MMI  $\geq 24\%$ .

Apart from MMI there were no statistical significant differences in any of the continuous or categorical variables between those patients who died with an MMI above and below 24%. Only six of variables were found by logistic regression to be independent predictors of mortality (i.e. age, MMI, Simple Clinical Score, a discharge diagnosis of cancer, a hemoglobin below 11 gm%, and prior illness that required the patient to spend more than 50% of daytime in bed) (Table 2).

SCS  $\geq 12$  predicted one year mortality with the highest odds (16.1, Chi square 79.09,  $p < 0.0001$ ). However, the AUROC of age combined with MMI as a predictor of annual mortality is 0.79 (95% CI 0.72-0.85), and is comparable to the AUROC of the SCS (0.82, 95% CI 0.76-0.88). A score of age plus MMI  $> 104$  identified 69% of deaths, and 43% the 119 patients who

exceeded this score were dead within a year (odds ration 9.4, Chi square 73.50,  $p < 0.0001$ ). Quartiles of this simple score distinguished patients with a very low (3%) annual risk of death (i.e. age plus MMI  $< 74$ ), a low (7%) risk (i.e. age plus MMI  $\geq 74$  to  $< 91$ ), an intermediate (15%) risk (i.e. age plus MMI  $\geq 91$  to  $< 106$ ) from those with a very high (41%) risk (i.e. age plus MMI  $\geq 106$ ) (Figure 3). A more precise estimate of survival at one year can be made from the formula  $1/1+e^{-z}$ , where  $z$  is  $-8.2476 + \text{age} * 0.0806 + \text{MMI} * 0.0275$ .

## Discussion

A predictive score's performance is measured by determining its discrimination, calibration and universal validity. Compared with other predictive mortality scores the SCS provides accurate predictions, excellent discrimination between survivors and non-survivors (16), and has been validated in diverse clinical settings (3-6). This study demonstrates that the SCS retains its discrimination for up to one year after hospital admission. It also suggests that ECG-DM is a significant independent predictor of annual mortality, which when combined with age has comparable discrimination to the SCS. Although the standard 12 lead ECG is a highly sensitive means of ruling out the risk of in-hospital mortality in acutely ill medical patients (7), the influence of slight ECG abnormalities on mortality risk has not been adequately quantified. MMI, on the other hand, is reported as a continuous variable that increases as the risk of death rises.

This small study of a convenient sample of patients is obviously limited. Doubtless a larger study would have detected more than six independent predictors of mortality and would have yielded more accurate comparisons of their relative predictive power. This study was performed just before services in the hospital underwent reconfiguration part of which was the diversion after midnight of seriously ill patients directly to Limerick Regional Hospital. The overall mortality rate of 3.5%, therefore, was comparable to the in-hospital mortality observed in both hospitals over the last 10-15 years. The patients studied represent those patients that could be seen promptly after their arrival in hospital. Since the authors worked a one-in-four 24 hour roster and 27% of admissions were studied the patients represent most of the patients the authors cared for. It is possible of course that ECGDM would not be able to predict mortality so accurately in a different patient population. However, we are currently following a cohort of 99 cardiac out-patients with a lower mean MMI than our study population (17% SD 9% versus 23.0% SD 13.5%,  $p < 0.00001$ )- after one year of follow-up the only patient that has died was the one with the highest age+MMI score of 124 (i.e. age 89 + MMI 35% ).

The MMI is more than likely a proxy for cardiac disease. The MMI reflects abnormalities in the myocardium at a metabolic level, which may include ischemia and other causes. It is important to stress that it should not be relied upon for diagnostic purposes. Of 19 patients who had acute

myocardial infarctions six had normal MMI values (i.e. <20%) early in their presentation - two of these patients had obvious classical acute ischemic changes on 12 lead ECG at the time ECG-DM was performed (11). An ECG-DM, therefore, is not diagnostic but a non-specific indicator of myocardial health. Measurement is carried out not only directly on an ECG-signal but also indirectly by examining the asymmetry of the ECG signal between the right and left ventricles, which allows signal averaging to be obtained within 30 seconds. From the six traditional ECG leads of I, II, III, aVR, aVL and aVF patented formulae determine asymmetry of the ECG signal between the ventricles in very a short time (8,9). This signal is highly accurate and correlates with the amplitude of micro-alternations not only of the T wave but of the entire PQRS complex. This method is much more sensitive than direct “beat to beat” measurement of ECG micro-alternations, and this allows measurements to be performed at rest. Although other techniques might diagnose cardiac disease better than ECG-DM, 1 year mortality is most likely related to the severity of disease rather than diagnoses per se. Unlike clinical opinion and other diagnostic techniques ECG-DM is objective, quick, easy and cheap to perform, and does not require any skill or training to interpret.

Prognostication has been recognized as an important but often neglected part of patient management (17). Acute hospitalization, especially of the elderly, is an opportunity to recognize patients at risk of imminent decline and mortality, and make appropriate arrangements in keeping with their wishes (18). As much as a quarter of the costs of health care are spent in the last year of life (19). If this money is to be spent wisely care should be planned in advance with attention to symptom management, caregiver support, so that the resources available are efficiently directed to the needs and desires of the patient (20,21).

Other prognostic indices are available to predict mortality in hospitalized older adults, but their use has not been incorporated into routine medical practice (1). Some existing models are applicable only to specific patient populations and disease states (22-24) or require subjective assessments of risk by clinicians (25). Others require use of lengthy formulas (26) or knowledge of certain laboratory data and functional status (27,28), which are not always available in a patient’s chart (29). This study suggests that the SCS has a comparable performance to other more sophisticated tools (22,26). Even though already contained in the SCS, time in bed was also

an independent predictor of mortality at one year. This indicates that the weighting given to time in bed by the SCS requires readjustment to more accurately predict one year mortality.

The finding that MMI is predicts one year mortality independently of age indicates that it is not just a proxy for age. Moreover, a combination of age and ECGDM quickly and objectively identifies within seconds of admission to hospital a substantial cohort of acutely ill medical patients who have a greater than 40% risk of being dead within a year, which translates into a life expectancy of 1.5 to 1.7 years. This information should prompt clinicians to initiate discussions on advance care planning and goals of care in their patients.

## **Conclusion**

1. The SCS retains its discrimination (AUROC 82%) for mortality prediction of acutely ill medical patients up to one year after admission to hospital.
2. ECG-DM combined with age has comparable discrimination for one-year mortality prediction to the SCS, but is quicker, cheaper and easier to perform. It also requires no skill to interpret.

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### **Conflict of interest**

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## Figures

Figure 1: Mortality at 365 days of patients according to their Simple Clinical Score (SCS). Only seven out of 162 patients with a SCS  $\leq 4$  died: four had cancer, one liver failure and two heart failure with MMI values of 40% and 50%.

Figure 2: Mortality at 365 days of patients according to their Myocardial Micro-alternation Index (MMI).

Figure 3: Kaplan-Meier survival curves for 365 days of patients according to quartiles of their age combined with their Myocardial Micro-alternation Index (MMI). One quarter of patients had a very low (3%) annual risk of death (i.e. age plus MMI  $< 74$ ), one quarter a low (7%) risk (i.e. age plus MMI  $\geq 74$  to  $< 91$ ), one quarter an intermediate (15%) risk (i.e. age plus MMI  $\geq 91$  to  $< 106$ ) and one quarter a very high (41%) risk (i.e. age plus MMI  $\geq 106$ )

### **Clinical significance**

- The Simple Clinical Score (SCS) is a reliable independently validated predictor of in-hospital mortality
- ECG-DM is a novel technique that reports abnormal low amplitude ECG oscillations as the myocardial micro-alternation index (MMI).
- The SCS and MMI plus age were comparable predictors of one year mortality
- SCS and ECG-DM are clinically useful for prognostication. ECG-DM is cheap, quick and easy to interpret.