

ULRR

The Erne mobile intensive coronary care study mortality, survival and MICCU

Item Type	Article
Authors	Donnelly, Michael;Mackenzie, Gilbert
Citation	Irish Journal of Medical Science; 191,pp. 175-185
Publisher	Springer
Download date	2026-05-15 07:57:51
Item License	https://creativecommons.org/licenses/by-nc-sa/1.0/
Link to Item	https://hdl.handle.net/10344/10322

The Erne Mobile Intensive Coronary Care Study Mortality, Survival and MICCU

Donnelly · and MacKenzie

Received: date / Accepted: date

Abstract This paper deals with the analysis and interpretation of data relating to mortality and survival in the first year of operation of the Erne MICCU study in Co. Fermanagh.

Aims: We aimed to measure in-hospital mortality from AMI, on WHO criteria, identify factors influencing mortality and survival and assess the performance of the MICCU.

Methods: All first admissions of suspected AMI to the CCU from the Fermanagh District in 1983-84. Some 297 patients were analysed. We recorded: demographic data, previous history of heart disease and co-morbidity, status of the current attack, delay to CCU, treatment and outcome. In total, 28 variables grouped as: (a) basic risk factors (18) and (b) clinical and treatment risk factors (10), were analysed.

Outcomes: In-hospital mortality and survival and performance of the MICCU.

Results: There were 329 admissions to the CCU of all types of which 297 (90.3%) were first admissions. Of the 297, 170 (57.2%) had AMI on WHO criteria and 42 (14.1%) were dead at discharge. Crude, 28 day, mortality (and unadjusted survival were statistically significantly worse in the AMI group. The multi-factor mortality analysis identified 5 variables influencing death at discharge. In relation to multi-factor survival, the MPR Weibull model identified a set of 9 variables in which the treatment variables pre-dominated over basic risk factors. The MICCU delivered patients to hospital statistically significantly earlier (5 hours on average) than other modes of transport, but did not prevent more deaths than the ordinary ambulance.

Conclusions There was no evidence of a direct, statistically significant, beneficial MICCU effect in either of the multi-factor mortality or survival models. However, the performance of the MICCU, measured in terms of crude survival, resulted from an adverse case-mix, which, when controlled for, suggested a small MICCU benefit. The findings relate to the first year of operation of the Erne MICCU study and may improve in later years.

Keywords Clinical Epidemiology · CCU · MICCU · Mortality · Prospective Study · Survival

M. Donnelly
Durham
Tel.: 07786825366
Fax: 07786825366
E-mail: ddddonnelly@hotmail.com

G. MacKenzie
Centre of Biostatistics
University of Limerick
E-mail: gilbert.mackenzie@ul.ie

1 Introduction

The Erne Mobile Intensive Coronary Care (MICCU) Study was conducted in Fermanagh, Northern Ireland, during 1982-90. The study data had been misfiled and were in storage for 30+ years. They have only recently been discovered and analysed. This paper deals with 1983-84, the first year of operation, and the analysis affords further insight into the effect of mobile intensive coronary care on mortality and survival in rural Ireland.

At that time death rates from Ischaemic Heart Disease(IHD) in Northern Ireland were among the highest in the world. Calculations by Pedoe (1982)[1] demonstrated that the age-standardised mortality rate was still increasing despite declines observed in England and in the New World. It was Pemberton et al (1963), in an internal memorandum ¹ who first focussed attention on the increasing mortality from IHD (later CHD) in Northern Ireland. See also, Trends in CHD: 1961-2011 [2] and Table 1 [3].

Consequently, Pemberton initiated a prospective epidemiological study of Coronary Heart Disease (CHD) in 1202 disease-free, middle-aged, men in six general practices in Belfast, Northern Ireland. The five year follow-up findings in relation to incidence and mortality were reported by Greig et al. (1980)[4]. Subsequently, further studies, investigating how risk factors in the population influenced trends in incidence and mortality from CHD, were mounted (MONICA, 1983; PRIME 1998)[5][6]. Recently, Pemberton's original 1202 middle-aged men study was extended by MacKenzie (2017) [7] who showed that the findings were consonant

¹ Department of Social and Preventive Medicine, The Queen's University of Belfast.

Table 1: Age-standardized Mortality Rate (per 100,000 pop. aged 40-69 years) and Rank, for Males and Females in selected countries in 1980.

Country	Males		Female	
	Rate	Rank	Rate	Rank
N. Ireland	630	1	191	2
Scotland	592	2	208	1
Ireland	499	3	160	4
E & W	482	4	136	5
N.Z.	468	5	178	3
Czech.	438	6	132	8
Australia	421	7	133	7
Hungary	410	8	134	6

Source: Uemura K and Pisa Z. (1985) - see text.

with the major North American prospective studies (Pooling Project, 1989).[8].

Clinical efforts in Belfast, in the early 1980s, were focussed mainly on Coronary Care Units (CCUs) and on Mobile Intensive Coronary Care (MICCU). It was Frank Pantridge who pioneered this life-saving approach. Pantridge (1967)[9] argued that mortality would be reduced by the prevention of sudden death due to myocardial infarction (MI) and that mortality and morbidity would be reduced by limiting the area of myocardial ischaemia (see Beaglehole (1986)[10] for example). As evidence supporting Pantridge's hypothesis accumulated, curiously, cardiologists in the United Kingdom remained relatively unconvinced (Julian, 2001)[11].

In NI, coronary care was then concentrated on the East of the Province. Accordingly, patients suffering an acute event in the West, often had to travel to Belfast (80 miles away) for treatment. There was a clear need for a modern coronary care Unit in the West. Accordingly, it was decided (by the first author and colleagues) to establish a CCU unit in

Enniskillen which would meet local needs. Given the nature of the rural terrain in Fermanagh this would need to be augmented by a Coronary Ambulance Service.

In 1983 a CCU was established at the Erne Hospital² and began admitting patients in November 1983. In deciding to set up a CCU service the clinicians involved resolved to monitor its activities and evaluate the performance of their mobile unit.

Below we describe the study in more detail focussing on the first year of operation. Our main analysis deals with identifying factors influencing in-hospital mortality and survival amongst first admissions to the CCU. We also quantify the effect of the MICCU service on these outcomes.

2 Patients and Methods

The study falls naturally into three sub-studies:

(1) All cases with suspected acute myocardial infarction (AMI) attending the CCU, (2) All such cases admitted to the CUU and (3) All *first* admissions to the CCU. It is worth noting that data in sub-study (2) are similar to episodes, where the records therein may be repeated measures on the same patient (readmissions), whereas, the data in sub-study (3) comprise different patients, independent one from the other, as required for conventional statistical analysis. Accordingly, below we describe the methods for sub-study (3).

2.1 Questionnaire

A detailed questionnaire was completed on all such patients and documented information on patient identification, past medical history and treatments, presentation of symptoms, diagnostic clinical data, current treatment, delays to treatment and care, prognosis and survival. Up to

² South West Area Hospital (SWAH), since 21st. June, 2012.

145 variables were recorded on patients admitted to the CCU with suspected AMI. Only a subset of key variables are considered for analysis in this paper. A copy of the questionnaire is available from the first author.

2.2 Entry Criteria

First admissions to the Erne CCU in Enniskillen with suspected Acute Myocardial Infarction occurring in one calendar year.

2.3 Period of the Study

The study considered here ran from November 15th. 1983 to November 15th. 1984 and represents the first year of operation of the Erne CCU and MICCU. The main study was, however, maintained for several years thereafter and annual data are now available from 1984 to 1990, and beyond.³

2.4 Population Studied.

The Population of Fermanagh and South Tyrone to Fivemiletown inclusively. It comprised an intended catchment area of Erne to Fivemiletown (Parliamentary Constituency) which we refer to as Fermanagh District. The background mortality rate (per 1000 population) from IHD (ICDs 410-414) in Fermanagh in three years relevant to the study period were: 2.82 (1971), 3.08 (1981) and 4.27 (1984). There is an obvious increasing trend in mortality from IHD.

A heart attack register was established in County Fermanagh and all episodes of suspected myocardial infarction occurring amongst current residents of the county and neighbouring areas within the study area and coming to the attention of the CCU were investigated. From the subsequent admissions to the CCU, only first admissions were selected for this study. The methodology adopted was that developed by McIlwaine and Donnelly (1985).[15]

³ These data will form the basis of further communications.

2.5 Outcomes

This is an observational study and not designed to meet minimal clinical differences in outcomes as in a randomized controlled trial. There are four measures of outcome of interest, namely:

- Numbers with AMI
- Mortality at discharge (alive/dead)
- In-hospital survival (number of bed-days)
- Performance of the MICCU

In this study we are able to identify factors influencing mortality at discharge and in-hospital survival and we investigate these relationships in detail below.

2.6 CCU and MICCU

The MICCU was modelled on the existing MICCU in the Ulster Hospital Dundonald. The CCU had four coronary care beds, centrally located around a nurse monitoring station, with an additional two monitoring beds and five telemetry beds. The CCU is within easy reach of the intensive care unit and is well equipped. A defibrillator and an emergency trolley carrying drugs and instruments is always available centrally. This equipment is checked daily by staff nurses. Similar equipment is available for the mobile unit which is a specially equipped estate car manned (24/7/365) by a fully trained Senior House Officer or a Registrar (ex Regional Medical Cardiology Centre (RMCC) in Belfast) and a fully trained staff nurse, competent in radiotelephony and local geography⁴.

Amongst other equipment carried was a twelve lead ECG machine and resuscitation equipment. The vehicle is usually summoned by a general practitioner or a close relative who may use a direct telephone line to the coronary care unit. The staff nurse on duty takes the initial details and decides if the call should be referred to the duty doctor. The doctor assesses the call and on deciding to respond takes careful and accurate details of the directions to the location of the patient and despatches the MICCU.

⁴ Roles adopted in subsequent years by paramedics.

2.7 ECGs

In relation to ECGs these were initially recorded by the MICCU team and very occasionally by a GP, usually in 12-lead strip form and then on A-4 when a computerized ECG machine was available. The ECGs were photocopied for the questionnaire and Minnesota coding rubrics were used to abstract Q waves, ST segments, T waves, BBB, axis deviation and hypertrophy in order to complete variables leading to the categorization of AMI by WHO (1979) criteria.[13] Doubtful ECGs were presented to the cardiologist, the research team, or a group of senior cardiologists at the RMCC by mail. At intervals, ECGs were blindly re-assessed for the purposes of quality control.

2.8 AMI Diagnostic Criteria

The diagnosis of AMI was based on the World Health Organisation's definition (WHO 1979)[13]. All suspected episodes were classified as follows: 1. Definite MI, 2. Possible MI, 3. Not MI, 4. Insufficient information. Details of the criteria are given in Appendix 1. The WHO definition of definite MI was programmed directly from the variables recorded in the study questionnaire and used throughout this study.

2.9 Risk Factors

These were grouped as follows.

Basic Risk Factors

Sociodemographic risk factors included: age at entry to the study (years), date of birth, sex (female, male), the Registrar General's Classification of Occupations (HMSO, 1970)[14], marital state (single, married, widowed, divorced, separated, other) and County of residence, coded as proximity (Fermanagh, other Co.).

Other important risk factors recorded: height (cms.), weight (kgs.), BMI (kg/m^2), smoking status (non, current, ex), systolic blood pressure (mm Hg), history of diabetes, hypertension, angina, family relative, previous infarct (absent, present), place where the infarct occurred (various settings), and Transport to the CCU (MICCU, Ord. Amb., Other). Total delay (in hours) from the onset of the attack to first admission to the CCU was also analysed.

Clinical and Treatment Factors

Place of arrival (AE, ward, CCU) and status on arrival (alive, dead) were recorded. A history of pain (typical, atypical, none) and the result of the ECG (Definite, Equivocal, Not MI) were noted. Enzyme levels, peak creatine kinase (CPK) and aspartate aminotransferase (AST) were also measured in IU/L. The use of par-enteral analgesia, or cardiac pulmonary resuscitation (CPR), or treatment for cardiogenic shock or cardiac pacing (yes, no) were recorded as well as the presence or absence of heart failure and life threatening arrhythmias (VT, VF, Others). We also recorded whether direct current cardioversion (DCC) was required in or out of hospital.

'Prevented' Deaths

In addition to the assessment of morbidity of those patients admitted by different modes of transport, the effect of the MICCU on mortality from IHD was assessed by quantifying the numbers of patients whose premature deaths were, *presumably*, avoided by the resuscitative intervention (McIlwaine and Donnelly, 1986)[15] This would usually involve correction of ventricular fibrillation by a combination of cardio-pulmonary resuscitation, counter current shock and possibly intravenous drugs. Thus, for the purposes of this study the definition of prevented death was a person: (a) resuscitated from primary or secondary ventricular fibrillation by means of cardiac-pulmonary resuscitation, or (b) counter current shock or (c) intravenous therapy.

Missing Data

Some missing data were encountered in continuous and categorical variables studied here. Missing data in the continuous variables were imputed by multiple linear regression methods assuming that the relationship between the complete data would hold for the missing data (the 'missing at random assumption'). For categorical data there were typically very few missing observations and these have been included in 'Other' categories or, rarely, omitted from the analysis.

Data Handling

For the first year completed questionnaires were conveyed monthly to Mrs. Iris Hay, in the data processing unit in the Department of Community Medicine, The Queen's University of Belfast, and input by her staff to their PDP-11/34A mini-computer. The data were checked, using stan-

dard range and nonsense checks in the SPSS-11 statistical package and stored on hard disc. Later, when the CCU in the Erne hospital acquired a Digital Equipment Corp. micro computer and a data manager, Dr. E. Turkington, the 83-84 data were transferred back to the Erne CCU on floppy disks. Eventually, with the rise of the PC, the accumulating study data migrated to diskettes which were MS-DOS compatible.

2.10 Statistical Methods

A variety of conventional statistical methods were employed. Single-factor analyses in relation to outcome (e.g., mortality) involved the comparison of means (t-tests) and proportions (chi-squared tests). Multi-factor analysis of mortality required the use of the multiple logistic function (Cox, 1970) [16] in which the probability of death ($Y = 1$) is given by

$$Pr(Y = 1) = \frac{\exp(x'\beta)}{[1 + \exp(x'\beta)]} \quad (1)$$

where $x' = (x_1, \dots, x_p)$ is a row vector of covariates for a patient and β is a column vector of p parameters measuring the influence of the covariates on the probability of death. The parameters were estimated by the method of Maximum Likelihood (ML) using the binary logistic regression procedure in SPSS (Version 26).[17]

Single factor survival analyses for categorical variables was carried out using the Kaplan Meier [18] procedure in the same package. For continuous variables and for multi-factor analyses (with continuous and categorical variables) the Cox regression (Cox, 1972) [19] procedure was used, again in SPSS (Version 26). Categorical variables were given appropriate design matrix representations in these analyses See Peng and MacKenzie (2014) [20] for information on the choice of appropriate reference subclasses. The PH assumption was checked using the Weibull Multi-Parameter Regression (MPR) Survival model which is not a proportional hazards model (Burke and MacKenzie, 2017) [21]. The hazard function for the Weibull distribution is

$$\lambda(t) = \lambda \gamma t^{\gamma-1} \quad (2)$$

where $\lambda > 0$ is the *scale* parameter and $\gamma > 0$ is the *shape* parameter. The MPR specification is then $\lambda = \exp(x'\beta)$ and $\gamma = \exp(x'\alpha)$ i.e., one

Table 2: Rank of Admission

Rank	Frequency	%
1	297	90.3
2	27	8.2
3	4	1.2
4	0	0.0
5	1	0.3
Total	329	100

predictor for the scale and another for the shape - unlike Cox model, which supports only $x'\beta$. The model was fitted by ML in the R [22] software package `mpr` (Burke, 2016)[23].

The conventional level of statistical significance ($p < 0.05$) is used throughout the paper as an indicator of a potential effect.

3 Results

During the period of the study there were 385 (100%) contacts with the CCU. Of these contacts, 329 (85.5% of 385) were admitted to the unit and out of these admissions, 297 (77.1% of 385) were first admissions ie, different individuals. Of the 329 admissions, 90.3% were first admissions. Accordingly, 32 (9.7% of admissions) were re-admissions. The rank of re-admission is shown in Table 2, surprisingly one patient, a 56 year old man with a final diagnosis of AMI, was admitted 5 times during the year. However, our main interest lies in analysing outcome in the 297 individuals who were admitted to the CCU for the *first* time during 83-84.

3.1 Overall Outcomes

Of the 297 first admissions 170 (57.4%), approximately two thirds, were diagnosed as AMI, 109 (36.7%) as Possibles and

Table 3: ECG site of infarction in 170 AMI patients

ECG Site	No.	%
Anterior	60	35.3
Inferior	40	23.5
Sub Endo.	41	24.1
LBBB	7	4.1
Indefinite	7	4.1
Not ECG	15	8.8
Total	170	100

18 (6.1%) as Not MI. As only live patients were admitted to the CCU there was information on all patients.

Table 3 shows the observed distribution of the ECG site of infarct in the 170 AMI patients. The distribution differs from that observed in the contemporaneous studies in Omagh and Ballymena, Mathewson et al. (1985)[30]; by exhibiting a higher proportion subendocardial infarcts and slightly lower proportions of anterior and inferior infarct. Some 8.8% were diagnosed on non-ECG criteria - see the WHO criteria for AMI (Appendix 1).

Separately, 42 (14.1%) of the first admissions were dead at discharge and 255 were alive. All but 3 of the 42 deaths (93%) occurred within 28 days of admission so that our study data are comparable to studies focussing on 28-day mortality.

The relationship between AMI and death was investigated by means of a two-way contingency table. In the AMI group 32/170 (18.8%) were dead, in the Possible group 7/109 (6.4%) and in the Not MI group 3/18 (16.7%) ($\chi^2 = 8.51$, $df=2$, $p = 0.014$).

Table 4: Erne MICCU Study: comparison, of the means of continuous factors measured at admission, between patients discharged alive and dead.

Variable	Alive		Dead		Test		
	Mean	SE	Mean	SE	t	df	p
Age	61.43	0.80	67.81	1.42	-3.12	295	0.002
Height	166.86	0.58	167.64	1.06	-0.52	295	0.521
Weight	69.88	0.84	69.95	1.62	-0.03	295	0.970
BMI	25.03	0.25	24.88	0.50	+0.24	295	0.810
SBP	141.49	1.89	123.14	5.90	+3.49	295	0.005
log _e (CPK)	5.53	0.85	6.29	0.23	-3.33	295	0.001

NB: Variances differ significantly in all but BMI & SBP. There are two high values of SBP in the dead group which elevate the s.e. but the test of variances is not statistically significant. Probabilities are for separate variances where they differ

Table 5: Erne MICCU Study: relationship between mortality and 12 basic categorical risk factors considered singly

Variable	Dead at Discharge			pr($\chi^2 \geq \text{obs.}$)
	No. Dead	% Dead	Total	
<i>Sex</i>				
Male	29	15.6	186	$p = 0.353$
Female	13	11.7	111	
<i>Marital State</i>				
Single	38	20.8	48	$p = 0.343$
Married	159	12.6	182	
Other	58	13.4	67	
<i>Proximity</i>				
Fermanagh	39	14.6	267	$p = 0.492$
Other Co.	3	10.0	30	
<i>History of Infarct</i>				
Absent	32	13.9	230	$p = 0.834$
Present	10	14.9	67	
<i>History of Angina</i>				
Absent	22	15.5	142	$p = 0.522$
Present	20	12.9	155	
<i>History of Hypertension</i>				
Absent	28	13.5	207	$p = 0.645$
Present	14	15.6	90	
<i>History of Diabetes</i>				
Absent	33	12.4	266	$p = 0.012$
Present	9	29.0	31	
<i>Smoking Habit</i>				
Non-smoker	14	13.7	102	$p = 0.250$
Current smoker	13	11.0	118	
Ex-smoker	15	19.5	77	
<i>Family History of MI</i>				
Absent	38	16.7	227	$p = 0.021$
Present	4	5.7	70	
<i>Place of Onset</i>				
Home	29	13.8	102	$p = 0.637$
Work/Street/Rec.	6	12.0	118	
Other	7	18.9	77	
<i>Delay</i>				
<1 day	41	15.2	269	$p = 0.092$
1+ days	1	3.6	28	
<i>Transport</i>				
MICCU	20	19.4	103	$p = 0.161$
Ord. Amb.	12	11.8	102	
Other	10	10.9	92	

Table 6: Erne MICCU Study: relationship between mortality and 10 categorical clinical and treatment risk factors considered singly

Variable	Dead at Discharge			pr($\chi^2 \geq \text{obs.}$)
	No. Dead	% Dead	Total	
<i>Analgesia</i>				
None	11	7.3	150	
GP	13	22.8	57	
MICCU	7	25.0	28	
AE or CCU	11	17.7	62	$p = 0.006$
<i>Heart Failure</i>				
None	12	7.6	157	
GP-MICCU-AE	12	27.3	9	
CCU < 1h	6	13.6	44	
CCU > 1h	12	23.1	52	$p = 0.002$
<i>Arrhythmias</i>				
None	9	4.6	195	
GP-MICCU-AE	12	36.4	33	
CCU < 1h	7	35.0	20	
CCU > 1h	14	28.6	49	$p < 0.001$
<i>Atropine</i>				
None	18	7.0	257	
GP-MICCU-AE	7	50.0	14	
CCU < 1h	4	44.4	9	
CCU > 1h	13	76.5	17	$p < 0.001$
<i>CPR</i>				
None	18	6.7	268	
GP-MICCU-AE-CCU	24	82.8	29	$p < 0.001$
<i>CPR Delay</i>				
No CPR	18	6.7	267	
< 1 day	15	78.9	19	
1+ days	9	81.8	11	$p < 0.001$
<i>Rx for CGS</i>				
No	17	6.5	263	
Yes	25	73.5	34	$p < 0.001$
<i>Pacing</i>				
No	26	9.5	274	
Yes	16	69.6	23	$p < 0.001$
<i>Major ECG Abn.</i>				
Absent	31	11.4	273	
Present	11	45.8	24	$p < 0.001$
<i>In-Hosp. DCC</i>				
Absent	30	10.9	274	
Present	12	52.2	23	$p < 0.001$

NB: Small numbers required the grouping of some categories; when MICCU is grouped usually MICCU is the main contributor (but always < 10 deaths)

Turning to the last outcome, Figure 1 shows the in-hospital survival by AMI (lower curve): the survival of patients with a diagnosis of AMI is significantly worse ($\chi^2 = 5.21$, $df=1$, $p = 0.022$; logrank test). In the AMI group, survival at 28 days is approximately 64%, whereas it is approximately 84% in the non-AMI group. Note however by 50 days the survival is similar around 60-70%. However, the mortality pattern in the tail is based on very few events and subject to large standard errors. Accordingly, it is unwise to extrapolate beyond 30 days.

In relation to transport to hospital the MICCU performed well with statistically significantly better median transport times than by the ordinary ambulance route: MICCU, median= 2.58 hrs. and OA, median= 4.25 hrs. ($\chi^2 = 7.53$, $df=1$, $p = 0.006$). The pattern of delay is in Figure 2, which shows $\Pr(\text{Delay} > t)$ against time (t) and the lower probability of long delays by MICCU.

Some 31 (13.0%) prevented deaths were identified using study criteria: 14 (13.6%) were transported by MICCU, 14 (13.7%) by ordinary ambulance and 3 (3.3%) by other methods. There is no difference in the numbers of deaths prevented between MICCU and ordinary ambulance ($p > 0.05$).

3.2 Factors Influencing Mortality

Table 4 shows the mean levels of continuous variables measured at admission in those who were alive and dead at discharge. Only three of these, age, systolic blood pressure and the natural logarithm⁵ of CPK (the peak of the enzyme phosphocreatine kinase) show a statistically significant difference between the alive

⁵ Logarithm to the base e : the transformation makes the distribution more symmetric.

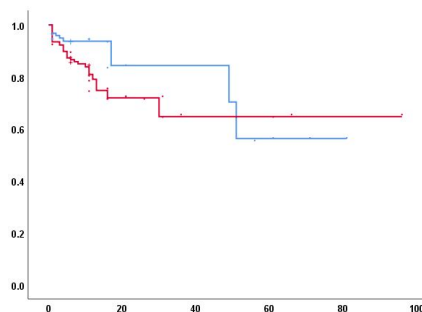


Fig. 1: In-hospital survival (Days) by AMI (lower curve) and non-AMI (upper curve)

and dead groups. Those who died were older, on average, by 6.4 years, had lower systolic blood pressures, by 18.4 mm Hg., on average and a higher transformed level of CPK.

Table 5 shows the distribution of mortality by 12 categorical variables considered singly. Of the 12, only 2 - history of diabetes and family history of MI - show a statistically significant association with mortality. Patients with pre-existing diabetes are at an increased the risk of death: 29.0% compared to 12.4% ($\chi^2 = 6.32$, $df = 1$, $p = 0.012$), while, patients with a family history of a previous MI are at a decreased risk: 5.7% compared to 16.7% ($\chi^2 = 5.36$, $df = 1$, $p = 0.021$).

Table 6 shows the results for the clinical and treatment variables selected for analysis. The picture presented is strikingly different with all of the variables exceeding the nominal level of statistical significance.

Multi-factor Analysis

The continuous and categorical variables in Tables 4, 5 and 6, respectively, together with the binary indicator AMI were included the MLF analysis which esti-

Table 7: Multi-factor Logistic Model: simultaneous solution using stepwise analysis

Variable	Coef.	s.e.	<i>p</i>
Intercept	-2.577	0.399	0.000
<i>Prev. MI</i>	-3.046	1.144	0.008
<i>Smoking</i>			
Current	-1.828	0.727	0.012
Ex-smoker	-0.254	0.637	0.689
<i>Atropine</i>			
GP-MICCU-AE	2.125	0.834	0.011
CCU < 1h	2.529	1.205	0.036
CCU ≥ 1h	2.271	0.846	0.007
<i>CPR</i>			
Yes (anywhere)	3.173	0.776	0.000
<i>RX for CGS</i>			
Yes (anywhere)	2.630	0.653	0.000

The reference categories above are always 'None', 'Non' or 'Not Given' as appropriate: their regression coefficients (not shown) are zero.

mated the probability of death at discharge. Stepwise forwards and backwards analyses were conducted. In both cases the solutions were similar and Table 7 shows the final result for the forward solution. Only 5 of the 29 variables studied were statistically significantly related to the probability of death. These were: Previous MI, Smoking History, Administration of Atropine, Cardiac Pulmonary Resuscitation and treatment for Cardiogenic shock. However, interestingly, patients with a previous MI, or, who were current smokers, were at a lower risk of death on discharge, when the effects of the other three factors were taken into account. Comparing with Table 5: patients with a previous MI had a slightly higher risk of death, while current smokers had the lowest risk. Neither finding was statistically significant in Table 5.

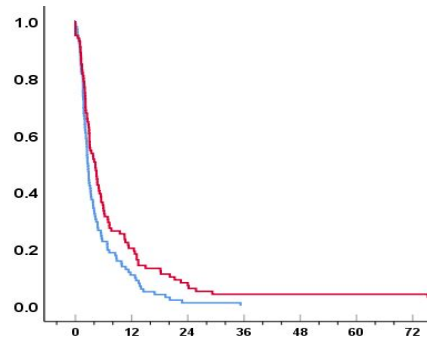


Fig. 2: Probability of Delay > *t* (hours) by *t* (time in hours) for MICCU (lower curve) and ordinary ambulance (upper curve) modes of transport.

The forward solution is very parsimonious involving only 5 variables, but its predictive power is quite impressive with a specificity of 95.6% and a sensitivity of 76.2%. The model implies a contingency tables with $(2 \times 3 \times 4 \times 2 \times 2 = 96)$ cells. If patient X has a previous MI and is a current smoker who did not need atropine or CPR or treatment for CGS, then $Pr(\text{death}) = 0.00058$. This is the minimum probability of death supported by the model. There were 13 cases satisfying these clinical criteria and none were dead at discharge. That the model provides a reasonable fit to the data is also evidenced by the Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 2.03$, $df=6$, $p = 0.917$.

3.3 Factors Influencing Survival

We analysed the same variables (Tables 4, 5 and 6) in relation to survival using a combination of Kaplan Meier, Cox regression and the more general Weibull MPR model.

Of the continuous variables studied three of the six were found to be signifi-

Table 8: Cox Regression Analysis: continuous factors analysed singly

Variable	Coef.	s.e.	<i>p</i>
Age	+0.031	0.015	0.040
Height	+0.016	0.017	0.362
Weight	+0.003	0.012	0.791
BMI	-0.009	0.040	0.826
SBP	-0.020	0.006	0.001
log _e (CPK)	+0.021	0.834	0.049

NB: +signs increase the hazard and -signs decrease it.

cantly related to survival. The results are shown in Table 8. Only systolic blood pressure shows a strong relationship with survival and that, unsurprisingly, implies the higher the blood pressure the lower the risk of death.

Among the basic categorical risk factors (Table 5) the KM analysis showed that only two variables were statistically related to survival: patients presenting with a history of diabetes had significantly shorter survival ($\chi^2 = 8.25$, $df=1$, $p = 0.004$) and patients with a previous infarct had significantly better survival ($\chi^2 = 4.53$, $df=1$, $p = 0.033$). For the ten categorical clinical and treatment variables (Table 6), the picture is again completely different - all but Direct Current Conversion (DCC), show statistically significant relationships with survival. Due to space limitations we omit these single factor survival graphs. (They are, however, available from the second author).

Weibull MPR Modelling

We checked the validity of the Cox model by fitting the Weibull MPR model [16] and discovered that some the factors in Tables 4, 5 and 6 were not PH. Accord-

ingly, we adopted the Weibull MPR model which can cope with PH and non-PH data.

Table 9 shows the resulting stepwise forward solution for the Weibull MPR model. Nine variables are selected. Three of these appear in the shape parameter which means they are non-PH and could not therefore be satisfactorily modelled in a standard Cox model or, equivalently, in the standard Weibull PH model which we use as a natural surrogate for Cox model, for the purposes of comparison. A comparison of the AICs (Table 9) shows that the MPR is an improvement over the standard Weibull PH model which fitted 11 variables (some different from the MPR model, Table 7) in the scale.

The effect of the three variables in the shape parameter is to increase the hazard with time. In the case of place of attack, which, uniquely, appears in the scale and shape parameters, its effect in the scale is to reduce the magnitude of the hazard, thus improving survival, but later to attenuate this reduction with time.

From the scale parameter it is clear that patients with AMI, and/or who were married (or other) and/or who had their attack outside the home had better survival, while those who received CPR, Atropine, or Parenteral Analgesia had worse survival. The magnitude of the coefficients of the treatment variables (together with their statistical significance) suggest that these are the major determinants of survival in this study. We may refer to the composite effect of these latter variables as the *Severity of attack*.

We note that all the coefficients of the variables in Table 9 are adjusted for the effects of the other variables in the model and hence represent 'independent effects' - effects which are not explained by the other variables.

Table 9: MPR Weibull Regression Survival Analysis: stepwise forward solution - 9 variables

Variable	Coef.	s.e.	<i>p</i>
<i>Scale</i>			
Intercept	-4.913	0.743	<0.001
CPR	+3.225	0.605	<0.001
Atropine	+2.343	0.613	<0.001
P. Analgesia	+1.887	0.557	<0.001
ECG Abn	+1.435	0.534	0.007
WHO AMI	-2.024	0.665	0.002
<i>Marital State</i>			
Married	-1.781	0.576	0.002
Other	-2.217	0.718	0.002
<i>Place of Att.</i>			
Work/Str/Ent.	-0.586	1.134	0.605
Other	-4.620	1.536	0.003
<i>Shape</i>			
Intercept	-0.057	0.163	0.726
Diabetes	+0.821	0.130	<0.001
Age	+0.233	0.091	0.010
<i>Place of Att.</i>			
Work/Str/Ent.	+0.298	0.283	0.292
Other	+0.975	0.239	<0.001

NB: +signs increase the hazard and -signs decrease it; for this MPR model the AIC=329.51 compared with an AIC=331.7 for the equivalent Weibull PH model. The lower the better.

Figure 1 showed that the presence of AMI significantly decreases survival, but that after adjustment for case-mix the WHO AMI coefficient in Table 9 indicates AMI significantly improves survival. Recall that the result in Figure 1 emerges from the net, uncontrolled, interplay of the factors in Table 9.

MICCU

Despite the shorter transport times, during the study period (see Figure 2) there was no significant mortality or survival advantage attributable to the operation of the MICCU. The unadjusted model shows that, relative to MICCU, trans-

port by ordinary ambulance (coef. = -0.594, s.e. = 0.365) and other (coeff. = -0.563, s.e. = 0.387) leads to slightly better, but not statistically significantly better, survival (both coefficients are negative). However, allowing for case-mix, by fitting transport to the final stepwise forward (case-mix) model in Table 8, turns both of these coefficients positive (coef. = +0.517, s.e. = 0.504 : coef. = +0.448, s.e. = 0.532), respectively, suggesting worse survival than by MICCU.

4 Discussion

That the Erne Study data have now come to light means that an important part of the history of the development of MICCU services in Ireland can now be told. Inevitably, the study and its methods reflect the techniques prevailing at the time.

The use of the WHO's (1979) [13] definition for definite AMI was a key decision to ensure consistency within the study and to maintain comparability with the emerging International literature. This definition relies heavily on ECG criteria and enzymes which have evolved rapidly. Current guidelines pertain to patients presenting with ischaemic symptoms and persistent ST-segment elevation on the ECG. Of course, Stemi rubrics now decide management. Most of these patients will show a typical rise in biomarkers of myocardial necrosis (troponins) and progress to Q-wave myocardial infarction. In Erne, these developments were applied later, but not to the 1983/84 data. Nevertheless, the methods deployed in the Erne study are representative of studies of that era.

The Erne results show that the MCCU performed well, but that the *prevented* death comparison with the ambulance was disappointing. In the single factor anal-

ysis (Tables 5), those identified as influencing mortality are interesting for formulating preventive strategies. Given that youth, systolic BP and CPKMB were statistically and clinically important they suggest the need to identify young hypertensives in order to prevent AMI and cerebrovascular accident by direct oral anticoagulant. The importance of diabetes leading to metabolic syndrome compounded by family history (inversely) stresses the need for testing for DM and familial hypercholesterolaemia.

However, multiple logistic function identifies factors, the effects of which, cannot be explained by those contending factors eliminated from the model. Any orthodox interpretation of the findings indicates that prevention of the need for Atropine, CGS and parenteral analgesia is the most direct route to reducing mortality. We estimate from the model that, at least, a 50% reduction would be achievable if these factors were abolished. As each of these factors are likely surrogate markers for complications of MI such as complete heart block and/or ongoing ischaemia, the need for preventative revascularization therapy is emphasised.

We note that primary prevention was the aim of the parallel *Heartbus Project* which opportunistically screened subjects at Enniskillen Market, finding cholesterol in excess of 10 mmol/litre (NICHSA, 1985) [24]. Subsequently, this project has been succeeded by the *Our Hearts, Our Minds* project (Connolly, 2020).[25].

It was, however, surprising to learn that having had a previous MI and/or being a current smoker significantly reduced the risk of death confirming the single factor findings which, might otherwise, have been thought to have been due to an adverse case-mix. Whilst there is, some supporting evidence for the smoking ef-

fect from a prospective, multicentre, observational, study (Song, et al. 2019)[26], both of these findings warrant further detailed investigation.

Mortality and Survival are related, but different quantities. The Weibull MPR model identified a more diverse set of variables influencing survival than the logistic model found influencing mortality. The mortality model contains two basic risk factors, previous infarct and smoking, whereas the survival model contains age, marital state, and presence of diabetes. There is some similarity between the two models as the receipt of atropine and treatment for CGS increase the risk of death and worsen survival. Perhaps the most striking finding is the reversal of the effect of AMI due to case-mix in the survival analysis. Accordingly, survival would be improved substantially by abolishing the need for Atropine, CPR and treatment for parenteral analgesia.

In relation to diabetes mellitus the final mortality model excludes this factor, but the survival model includes it and the single factor analysis suggests its presence significantly increases the chance of death. Overall, the findings are suggestive of an effect. Its elimination from the mortality model might be explained by arguing that DM patients have more severe disease. We examined this hypothesis and found no statistically significant difference in the incidence of CPR, atropine and parenteral analgesia. We did however find that DM patients were 2.5 times more likely to experience cardiogenic shock (26% v 10%, $p<0.008$).

In Dublin, Gearty et al. (1971)[27] found that, over a three year period, 20 persons had primary ventricular fibrillation and, of these, 17 were successfully resuscitated outside of hospital. Whilst they did not focus on community mortality, their results showed that only 32%

had a response time under 2.9 hrs. but in the majority the delay between onset and first response was greater than 2.9 hrs. pointing, they argued, to the need for a paramedical response system. Subsequently, Mulcahy, et al., (1975)[28], studied 364 post-first MI (28+ day) survivors for 4 years and found that only severity of the initial attack was associated with poor long term survival. The introduction of mobile coronary care in Belfast in 1965 seems to had equal effects in reducing mortality inside and outside hospital (McIlwaine et al. 1986)[29]

Mathewson et al (1985)[30] compared mortality from MI in two areas in Northern Ireland over a 14 month period, one with a MICCU service (Ballymena) and one without (Omagh). In Ballymena, the median transit time was 2.25 hrs.(MICCU) and in Omagh 4.25 hrs. (ambulance), and in Erne the medians were similar, 2.6 hrs. (MICCU) and 4.25 hrs. (ambulance), despite traversing more disparate terrain. Overall, mortality from MI was estimated to be 63% in Omagh and 50% in Ballymena, whereas, on the same basis, the mortality in Erne was 14.1%. However, formal comparisons with this study are difficult since the WHO 1979 definition of AMI was not applied exactly. In addition, all first admissions to the CCUs were treated as infarcts, while in Erne, 6.1%, (95CI: 3.33% - 8.87%), were classified as non-MI. These issues and their rather limited analytical adjustment for case-mix, places their conclusion, that the lower mortality in Ballymena was attributable to the MICCU service, in some doubt.

In related work, Adgey et al. (1991)[31] showed, in Belfast, that patients with ventricular fibrillation without myocardial infarction had a worse prognosis. The authors identified: ventricular fibrillation, previous AMI, hypertension, and digoxin

on discharge as factors independently associated with increased mortality. While investigating options to prevent early deaths in acute myocardial infarction, Kirchberger et al. (2010)[32] showed that in one third, earlier preventive measures might have been effective.

Finally, we note that with increasing awareness promoting earlier presentation and prompting rapid re-vascularisation treatment strategies (such as PCTA/stenting), in-hospital mortality has fallen from the 83-84 levels to around 2% today, Kush (2008)[33] and Dégano (2015).[34]

Acknowledgements

We thank the people of County Fermanagh for their co-operation throughout the period of the study. In particular, we thank Professor Mahen Varma, and Dr. John Williams, Consultant Physicians and the junior medical staff at the Erne Hospital: Dr. Andrew McCarthy, Dr. John Kirby, Dr. Enda Chadwick, Dr. Paula Toner and Dr. Theo Nugent. Drs. E. Turkington and B. McAleer were also very helpful in relation to data processing. Invaluable support and co-operation was provided by Jenny Cecil, Maizie Fleming and Sisters O'Kane and McNiff and their staffs at the Erne hospital. The MICCU vehicle was donated by Lisbellaw Young Farmers Club and incidental expenses were provided by local research funds. Dr. Turkington was supported by Action for Community Employment (Ace) funding through the Northern Ireland Chest Heart and Stroke Association and by the Western Health Trust. Finally we thank the referees for their useful comments which improved the paper.

Appendix 1 - WHO Diagnostic Criteria for MI

A summary of the WHO Diagnostic Criteria for MI [12] follows:

1. *Definite MI*

- Typical ECG
- OR Equivocal ECG with definite enzymes
- OR Typical History with definite enzymes

- OR Positive post-mortem

2. Possible MI

- Remaining surviving cases with typical history including history of pain (typical or not)
- OR Fatal Cases with past history of chronic IHD
- OR Post-mortem evidence of chronic IHD

3. Not MI

- Remaining living cases notified
- OR Fatal Cases where another diagnosis made

4. Insufficient Information

- Remaining fatal cases notified

Declarations

Funding: The Study was supported by the Chest Heart and Stroke Association NI (Registered Charity), the Western Health and Social Services Board NI, via the Ace scheme, by the Lisbellaw Young Farmers Club and by Public donation.

Conflicts of interest: The authors have no conflicts of interest.

Ethics Approval: This study was conducted in accordance with the ethical standards of the NHS Western Health and Social Services Board and within the 1964 Helsinki Declaration and its later amendments. The study was approved by the REC of the Queen's University University of Belfast in 1982.

Authors' Contributions: The paper was drafted by the second author. Subsequently, both authors worked to improve the draft. The first author contributed to the Introduction and Discussion while the second author conducted the statistical analysis. Both authors were involved in interpreting the findings and refining the paper.

References

1. Pedoe, H.T. (1982). Report on the cardiovascular epidemiological unit: Initial programme, 1982 onwards. Internal Report, Ninewells Hospital and Medical School Dundee.
2. Scarborough, P., Wickramasinghe, K., Bhatnagar, P. and Rayner, M. (2011). Trends in coronary heart disease: 1961-2011. British Heart Foundation: London.
3. Uemura, K. and Pisa, Z. (1985). World Health Statistics Quarterly. Vol. 38:142-162.
4. Greig, M., Pemberton, J., Hay, I. and MacKenzie, G. (1980). A prospective study of the development of CHD in a group of 1202 middle-aged men, Journal of Epidemiology and Community Health, Vol. 34 (1): 23-30.
5. Evans, A.E., et al. (1983). MONICA PROJECT:Belfast Monica Project Manual of operations, The Department of Community Medicine, The Queen's University of Belfast, Mulhouse Annexe, Royal Victoria Hospital Site, Belfast, Northern Ireland.
6. Yarnell, J. (1998). The PRIME study: classical risk factors do not explain the several fold differences in risk of coronary heart disease between France and Northern Ireland. Prospective Epidemiological Study of Myocardial Infarction, Quarterly Journal of Medicine, Vol. 91(10):667-76.
7. MacKenzie, G., et al. (2017). Competing risk analysis of factors related to long-term incidence of CHD, J Epidemiol Community Health Vol. 71: 33–36. doi:10.1136/jech-2016-207347.
8. Pooling Project Research Group. (1978). Final report of the Pooling Project. J Chron Dis Vol, 31: 201–306.
9. Pantridge, J. F., and Geddes, J.S. (1967). A mobile intensive care unit in the management of myocardial infarction. Lancet, Vol. 2: 271-273
10. Beaglehole, R. (1986). Medical management and the decline in mortality from coronary heart disease. B Med J Vol, 292: 33.
11. Julian, D.G.(2001). The evolution of the coronary care unit. Cardiovascular Research Vol. 51: 621–624.
12. McIlwaine, WJ., Donnelly, MD., Chivers, AT, Evans, AE. and Elwood, JH. (1985). Certification of death from ischaemic heart disease in Belfast.(1985). Int J Epidemiol., Vol. 14(4):560-565. doi: 10.1093/ije/14.4.560.
13. WHO Special Report. (1979). Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease. Circulation Vol. 59 (3): 607-609.

14. Office of Population Censuses and Surveys (1970). *Classification of Occupations*, London, HMSO. NTC 5/1/157.
15. McIlwaine, W., Donnelly, MD., Malaghan, M., Chivers, AT., Evans, AE., Elwood, JH., Adgey, AJ., Campbell, NP., Geddes, JS. (1986). Deaths from ischaemic heart disease in Belfast. *Br Heart J.*, Vol. 55(4): 330-335. doi: 10.1136/hrt.55.4.330.
16. Cox, D.R. (1970). *The analysis of binary data*, London: Methuen.
17. IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y.), USA
18. Kaplan, E. L. and Meier, P. (1958). Non-parametric estimation from incomplete observations. *J. Amer. Statist. Assoc.* 53 (282): 457-481. doi:10.2307/2281868
19. Cox, D. R. (1972). Regression models and life tables (with Discussion). *J. R. Statist. Soc. B*, Vol. 34: 187-220.
20. Peng, D. and MacKenzie, G. (2014). Discrepancy and Choice of Reference Subclass in Categorical Regression Models. In: *Statistical Modelling in Biostatistics and Bioinformatics*. Editors: MacKenzie, G. and Peng, D., Springer, Munich, Germany.
21. Burke, K. and MacKenzie, G. (2017). Multi-parameter regression survival modelling - an alternative to proportional hazards, *Biometrics*, Vol. 73:361-716.
22. R Core Team. (2018). R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria.
23. Burke, K. (2016). mpr: Multi-Parameter Regression (MPR), R package version 1.0.2 (cran.r-project.org/package=mpr).
24. Cunnane, D. and Varma, MPS. (2012). Heartbus in Enniskillen. *Chest Heart and Stroke Association of NI Newsletter*, Vol. 1:1-2.
25. Connolly, S. (2019). Positive Health outcomes for Trust's 'Our Hearts Our Minds', *Health News, Derrydaily.net*(Sept).
26. Song, C., Fu, R. and Dou, K. et al. (2019). Association between smoking and in-hospital mortality in patients with acute myocardial infarction: results from a prospective, multicentre, observational study in China. *BMJ Open* Vol 9: 1-7, doi:10.1136/bmjopen-2019-030252
27. Gearty, GF., Hickey, N. Bourke, GJ. and Mulcahy, R. (1971). Pre-Hospital Coronary Care Service. G F Gearty, N Hickey, G.J Bourke, R Mulcahy. *British Medical Journal*, Vol. 3:33-35.
28. Mulcahy, R., Hickey, N., Graham, I. and McKenzie, G. (1975). Factors influencing long-term prognosis in male patients surviving a first coronary attack. *British Heart Journal*, Vol. 37: 158-i65.
29. McIlwaine, WJ., Chivers, AT., Donnelly, MD., Evans, AE. and MacKenzie, G. (1988). Fatal ischaemic heart disease in Belfast: a comparison of two community surveys. *Ulster Med J.*, Vol. 57(1):70-75.
30. Mathewson, Z. M., McCloskey, R.G. and Evans, A.E. et al. (1985). Mobile coronary care and community mortality from myocardial infarction. *The Lancet*, February 23rd., 441-444.
31. Dickey, W., MacKenzie, G. and Adgey, AJ. (1991). Long-term Survival After Resuscitation From Ventricular Fibrillation Occurring Before Hospital Admission. *Quarterly Journal of Medicine*, Vol. 803: 729-737, <https://doi.org/10.1093>
32. Kirchberger, I., Hunger, M., Stollenwerk, B., Seidl, H., Burkhardt, K., Kuch, B., Meisinger, C., Rolf Holle. (2010). Effects of a 3 year nurse-based case management in aged patients with acute myocardial infarction on rehospitalisation, mortality, risk factors, physical functioning and mental health. A secondary analysis of randomised controlled KORINNA study. *BMC Geriatr* Vol.10(3):1-17. e0116693. <https://doi.org/10.1371/journal.pone.0116693>
33. Kush, KK., Rapaport, F. and Waters, D. (2008). The history of the coronary care unit. *Can J Cardiology*. Vol. 21:(12) 1041-1045.
34. Dégano, IR., Veikko, S. and Veronesi, G., et al. (2015). Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations *Heart*. Vol. 101(17): 1413-1421.