Original Research Article

Complex changes in blood biochemistry revealed by a composite score derived from principal component analysis: effects of age, patient acuity, end of life, day-of week, and potential insights into the issues surrounding the 'weekend' effect in hospital mortality

ABSTRACT

Aims: To determine if a score (PCA score derived from Principal Component Analysis), a validated score of frailty and mortality, based on 12 blood biochemistry parameters can shed light on the issue of patient acuity, end of life and weekend mortality in hospitals.
Study design: The PCA score was calculated from over 280,000 blood tests. Average PCA score was calculated for different patient groups on different days of the week. An accompanying literature review of day-of-week variation in human mental and physical performance, and of studies investigating hospital mortality.
Place and Duration of Study: Retrospective analysis of 280,000 blood test results from 80,000 patients attending the Milton Keynes University Hospital in the interval January 2012 to July 2015.
Participants: Patients at outpatient clinics, the emergency department or as an inpatient who had one or more blood samples comprising the 12 biochemical tests.
Methodology: Average PCA score was calculated for patients in different hospital departments, on different days of the week, in different age groups, and at different times prior to death.
Results: The PCA score for individuals ranges from -6 to +6, with scores above zero generally associated with higher morbidity and mortality. The average PCA score is lowest in outpatient and A+E settings, varies across wards dedicated to different types of inpatient care, and is highest in ICU. The average PCA score reaches a minimum around age 18, and shows a modest increase with age in those who are not an inpatient. There is a day-of-week variance in the PCA score which is higher at the weekends, and dips to a minimum around Wednesday. The strength of the day-of-week effect varies by age and condition, and occurs in locations where staffing levels remain constant throughout the week.
Conclusions: Variation in human blood biochemistry follows day-of-week patterns and responds to different conditions, age, and the acuity of the condition. These add further weight to the argument that weekend staffing levels, and proposed 7 day working patterns, do not take account of all the factors that contribute to a day-of-week variation in hospital mortality and morbidity.

Keywords: Weekend mortality, day of week, blood biochemistry, mortality, morbidity, age, principle component analysis, critical care, inpatient care, emergency department

1. INTRODUCTION

In March of 2015 Cohen et al published an original article describing a PCA score (Principal Component Analysis) that represented a measure of frailty and risk of death based a large number of biochemical markers [1], that could be tailored down to 15 inexpensive and commonly performed blood tests (in Canada and the USA). With an algorithm that 'weights' the different tests appropriately, a resulting 'score' emerges that is predictive of frailty and mortality. However, only 12 of these tests are commonly available in the UK. The PCA score was kindly recalculated based on these 12 tests by Cohen and Moiressette-Thomas. It was then successfully re-tested for validity against their original dataset. The resulting composite score is best understood as the collective sum of weighted deviations from the average. The score therefore pivots about zero. Scores above zero represent a greater risk of frailty and mortality, and below zero a lower risk. As expected, there is considerable variation between individuals which necessitates the use of very large data sets to elucidate changes in population averages.

The rationale behind the pathological mechanism being measured is based on complex systems theory. No single marker was able to accurately monitor this ‘integrated albuminaemia’, which is generally associated with anemia, inflammation and low levels of albumin and calcium. The emergent PCA score suggests a ‘higher order or emergent physiological process’ is being measured [1].

In this large study, we used the adapted 12 test PCA score on our Milton Keynes University Hospital electronic database between the years of 2012 and 2015 comprising some 279,984 PCA scores for 80,424 patients. In our study we are testing the population average of the PCA score with recorded patient outcomes such as outpatient versus inpatient, specialty of care, age, death, and periods of ICU (Intensive Care Unit) care.

This analysis also enabled day of the week to be analyzed as an independent factor relating to the average PCA score in a variety of inpatient settings.

In the context of weekday staffing levels; data relating to patients seen in the accident and emergency department (A+E), and in the intensive care unit (ICU) enabled a reasonable assumption (that staffing levels did not vary by day of the week or weekend) to be made in interpreting the resulting data. In England, hospital mortality as it relates to the day of the week, most especially weekends, has been highly topical of late. This, following a publication by Freemantle et al [2] which has been linked to moves towards enhancing 7 day working in England. However, the link between mortality and hospital admission is complex, and needs to be understood in full before any conclusion can be drawn about causation. This latter point was emphasized in the comprehensive review by Becker [3], and it is unfortunate that many of the issues raised in this review have been overlooked in subsequent publications on this topic.

2. MATERIAL AND METHODS

2.1 Data Sources

The data available for this study came from three sources. The primary data source was from the pathology data base which provided details of internal hospital number, patient age, gender, ward/department and date of biochemistry tests. The internal hospital number was used to link the biochemistry results with patients who had died during an inpatient admission, as an alive/dead extract obtained from the hospital Patient Administration System. Finally, the internal hospital number was also used to locate details of patients who had died within 30 days of discharge via a Healthcare Evaluation Data (HED) data extract, this is a third party information system provided by the University Hospitals Birmingham NHS Foundation Trust.

2.2 Data Manipulation

Due to the progressive nature of the project various data extracts were grouped into three data sets. The first contained data from July 2014 to June 2015 (27,228 persons; 97,420 PCA scores), which was used for an initial feasibility study. This data set contains biochemistry test results for all inpatient admissions and A+E attendances. In this data set a complete patient history was generated for every person who died, and for persons having large numbers of repeat biochemistry requests. The second data set (53,196 persons; 182,564 PCA scores) expanded the time frame and scope to January 2012 through to June 2014, plus additional biochemistry test results for outpatient attendances. The focus of this data set was to generate a complete time profile for all patients with a large number of repeat biochemistry requests. (See Fig. A1 in the Appendix showing day-of-week profiles for 5 patients to illustrate that the day-of-week profile occurs in individuals). In the third data set (1,398 persons; 26,689 PCA scores) biochemistry test results for all persons having a stay in the intensive care unit were collected for every available patient contact (outpatient, inpatient and A+E between Jan-12 to Jun-14, and inpatient and A+E between Jul-14 to Jun-15). The focus of this data set was to generate a complete time history for patients having the highest number of repeat biochemistry requests during their time in intensive care.

Patients were categorized (as above) as either having a death in hospital during their final admission or alive at the point of last contact with the hospital during the study period.

Further analysis of these three data sets was conducted using Microsoft Excel with data extracted using the Pivot Table function in Excel. Microsoft Excel was used to create various charts and tables.

2.3 Missing Values

All test results undulate over time due to systematic factors, or due to measurement uncertainty. Patients will have multiple biochemistry tests, which on some occasions will contain missing values. On less than half of occasions between 1 and 7 of the 12 values can be missing. In this study missing values were not addressed via blind assignment of average values, but were added back via linear interpolation between adjacent values. Interpolation has not been used to create a score on those days when test results have not been requested, but only on those days when at least some test results are available. Hence, on those occasions when all 12 tests were not performed the time series of contacts for each patient was used to interpolate the missing values for that particular day. A linear relationship was assumed to interpolate any missing values. No attempt was made to interpolate missing values where there was an insufficient time history, indeed as discussed above; the emphasis was on obtaining a time series for patients with a high number of repeat test requests. RDW (Red blood cell Distribution Width), CRP (C Reactive Protein), ALP (Alkaline Phosphatase) and AST (Aspartate Transaminase) all undergo log transformation, and are therefore insensitive to any minor uncertainty due to interpolation – the latter three being the most commonly missing. These three tests also had the least impact on the PCA score due to a low weighting (Table 1), and hence uncertainty due to interpolation of results is minimised. See Table A1 in the Appendix for an example.

2.4 Statistical Evaluation

Patients were aggregated by different types of attendance/admission, and average PCA scores were calculated. The standard error of the mean (SEM) was calculated to give a 95% confidence interval (CI) for these averages (95% CI = 1.96 x SEM). The SEM = standard deviation ÷ the square root of the sample size. The SEM is especially appropriate when seeking to compare averages derived from populations where there is considerable variation around the average.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 The nature of the PCA score

Table 1 lists the 12 biochemical tests (along with the weighting parameters) which comprise the PCA score, and gives the weighted standard deviation as a measure of the relative contribution of each test to the overall score. As can be seen variation in Hb (Haemoglobin) and HCT (Haematocrit) make the biggest contribution while AST (Aspartate Transaminase) makes the least, except on the few occasions when this parameter reaches very high levels in certain types of inflammation. The unit transform converts UK units of concentration into the units used in the international studies, the log transform shows which tests are subject to a log 10 manipulations, while the weighting reflects the UK equivalent to that observed in the international cohort used by Cohen et al [1].

Table 1. Biochemical tests (and weighting parameters) comprising the PCA score and relative contribution to the overall score as measured by the weighted standard deviation for each test

Test	Unit Transform	Components of the Z-score			Z-score weight	STDEV of weighted values
		Log 10	Mean	STDEV		
Hemoglobin	0.1	No	12.144	2.208	-0.416	0.385
Hematocrit	100	No	36.236	6.009	-0.389	0.384
Albumin	0.1	No	3.281	0.745	-0.383	0.383
RBC	1	No	4.181	0.723	-0.344	0.347
Alb:Glob ratio	1	No	1.109	0.362	-0.339	0.313
RDW	1	**Yes**	2.69	0.142	+0.287	0.294
MCHC	0.1	No	33.456	1.489	-0.247	0.272
CRP	1	**Yes**	2.776	1.817	+0.289	0.259
ALP	1	**Yes**	4.419	0.526	+0.159	0.176
Platelets	1	No	277.275	129.214	+0.131	0.174
MCH	1	No	29.143	2.714	-0.16	0.168
AST	1	**Yes**	3.335	0.574	+0.022	0.027

RBC = red blood cell (RBC) count; RDW = red blood cell distribution width; MCHC = mean corpuscular hemoglobin concentration, MCH = mean corpuscular hemoglobin

Table 2 demonstrates that the average PCA score is sensitive to both the acuity and nature of the condition, i.e. differences between average score between outpatient specialties and inpatient wards. The Standard Error of the Mean (SEM) is shown as an indication of the uncertainty associated with the mean. Note that these are not always representative samples, but are only those patients that the clinician has deemed to require the full 12 biochemistry tests to assist in diagnosis or management. Scores for individuals vary from -6.0 to +6.0, i.e. the equivalent to ± 6 standard deviation equivalents of weighted biochemistry scores. The average PCA score varies from around +2.0 in the intensive care unit through to -2.0 in a variety of outpatient settings (average for outpatient departments is -1.25).

Table 2. Variation in average PCA score for different inpatient and outpatient departments (Jan-12 to Jun-14), where a clinician has deemed it necessary to request the full suite of 12 tests

Location	Average PCA Score	Standard Error of Mean	Sample size
Intensive care	2.16	0.02	5,034
Gastroenterology	1.17	0.02	7,422
Orthopaedic	1.14	0.03	2,543
Medicine	1.11	0.02	11,637
Endocrine/Haematology	1.10	0.02	8,780
Surgery	1.04	0.02	9,981
Respiratory/Cardiology	0.95	0.01	14,573
Antenatal/Gynaecology	0.80	0.04	680
Ante-Natal Assessment	0.66	0.02	1,537
Maternity Delivery	0.51	0.03	1,548
Ante-Natal OPD‡	0.46	0.07	184
Stroke Rehabilitation	0.44	0.03	3,213
Pediatric	0.12	0.04	1,735
Postnatal/Gynecology	0.10	0.08	1,088
Gynecology OPD	0.07	0.08	300

Coronary Care	0.01	0.05	1,640
Medical Assessment	-0.16	0.02	12,494
MacMillan Cancer OPD	-0.27	0.01	15,262
Ambulatory Care OPD	-0.46	0.02	7,435
Surgical Assessment	-0.49	0.02	9,693
Pediatric Assessment	-0.72	0.02	2,274
Neo-Natal Unit	-0.77	0.06	1,488
Infectious Disease Clinic OPD	-1.06	0.09	246
Orthopedic OPD	-1.15	0.10	230
Day Surgery	-1.20	0.06	225
Medical Oncology OPD	-1.20	0.04	843
Accident & Emergency (A+E)	-1.25	0.01	40,030
Diabetic Clinic OPD	-1.30	0.04	194
Ophthalmology OPD	-1.32	0.15	101
Hematology OPD	-1.34	0.03	3,008
Endoscopy OPD	-1.39	0.15	108
Cardiology OPD	-1.57	0.07	413
Angiography	-1.71	0.04	793
Dermatology OPD	-1.74	0.04	841
Neurology OPD	-1.93	0.09	137

‡ OPD = outpatient department

The stability of the average score can be assessed by comparing the value for intensive care in Table 2 (Jan-12 to Jun-14), with the same calculation derived from the Intensive care data set (Jan-12 to Jun-15) with 2.16 ± 0.04 (n = 5034) versus 2.23 ± 0.04 (n = 8936). On this occasion the 95% confidence intervals for the average are given, and these overlap. See Fig. A2 in the Appendix for the power law relationship between SEM and sample size. SEM for all averages in this study (where SEM or 95% CI are not shown) can be estimated from the power law relationship in Fig. A2. Fig. A2 illustrates that in the face of wide variation in PCA scores between individuals, sample sizes above 1,000 are required to give a reliable estimate for the average PCA score.

Fig. 1 shows the effect of age on the PCA score for patients attending A+E who had all 12 tests performed, but were not admitted to hospital. Data for this figure comes from the Jul-14 to Jun-15 data set. This group is the best proxy available for a moderately healthy population. The maximum PCA score (from the same data set) for all inpatients who died in hospital is also shown, to indicate generally higher scores for those who die. Investigation shows that low PCA scores in those who die are associated with sudden death such as aneurism, hemorrhage, major trauma, as opposed to a progressive disease. Note that variability in the PCA score between individuals reaches a minimum around age 10, while the population average reaches a minimum around age 20. There is also far greater variation between individuals who die than between individuals who are moderately healthy. The population average slowly increases with age but tends to rise more rapidly above age 75.

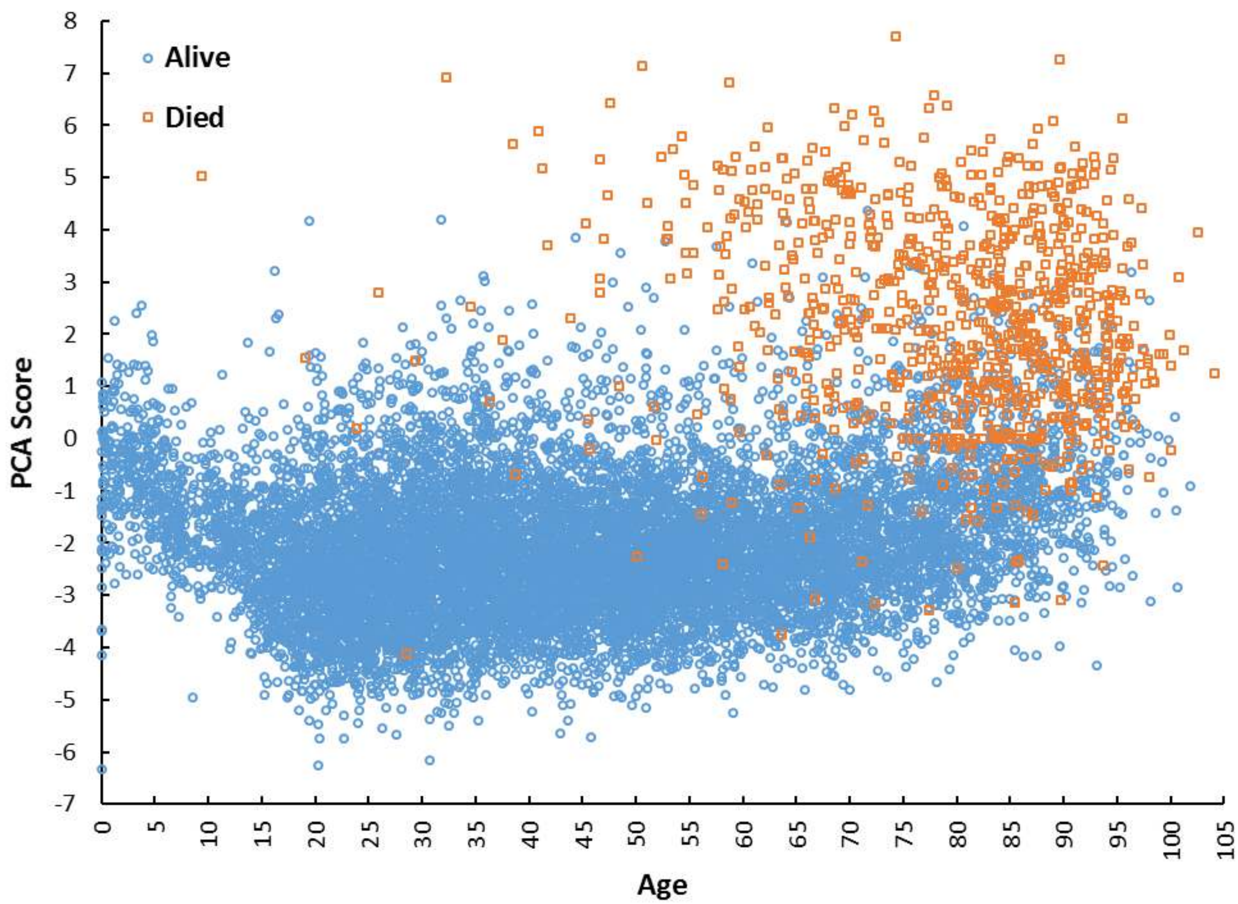

Fig. 1. PCA score for A+E attendance without inpatient admission (alive) versus highest PCA score in those who died during final inpatient admission (Jul-14 to Jun-15)

The last weeks of life represent a key period of general rapid decline in functional and immune status. Fig. 2 demonstrates that the average PCA score begins to rapidly increase (as a population average) around 26 weeks prior to death (combined data from all three data sets), and that this increase in population average PCA score is accompanied by increasing usage of inpatient services via bed occupancy. Around one year prior to death the population average for bed occupancy as around 44-times lower than during the last week of life. At greater than 20 weeks before death there is a slow decline in the PCA score to an asymptote at around 2 years (not shown). The trend upward at less than 20 weeks is not a general trend per se, but rather a composite picture of individuals experiencing both a general and a rapid increase in PCA score just prior to death. Fig. 2 also confirms the fact that from the viewpoint of individuals who die in hospital the vast majority of health service contacts (admissions and occupied beds) occur in the last weeks of life, *irrespective* of the age at death [4-5]. However, at an individual level this transition appears to be more abrupt with a sudden and permanent shift to a higher PCA score at some critical point prior to death (Fig. 3a).

For the individual in Fig. 3a their PCA score around 2 years prior to death is somewhat unstable ranging between 0.1 and 2.5, however it is higher than the scores for ‘healthy’ individuals seen in Fig. 1. Then follows a one-year period of frequent hospital care and a generally higher PCA score around 2.5. There is a period of seeming respite, however around 1 month prior to death there is a sudden transition to a permanently higher PCA score ranging around 3.0. This end-of-life transition is unique to each individual with some making this transition over a period of months. However, in all cases the final score is far higher than that seen at first contact (within the limits set by the time period of the study).

However, as Figure 3b illustrates some individuals can experience rapid deterioration where almost certain death is averted after treatment in the ICU. These individuals can then go on to make a seeming full recovery. The key observation here is that a calculated PCA score is useful to assess each individual's health status over extended periods of time, and especially when the score goes above zero.

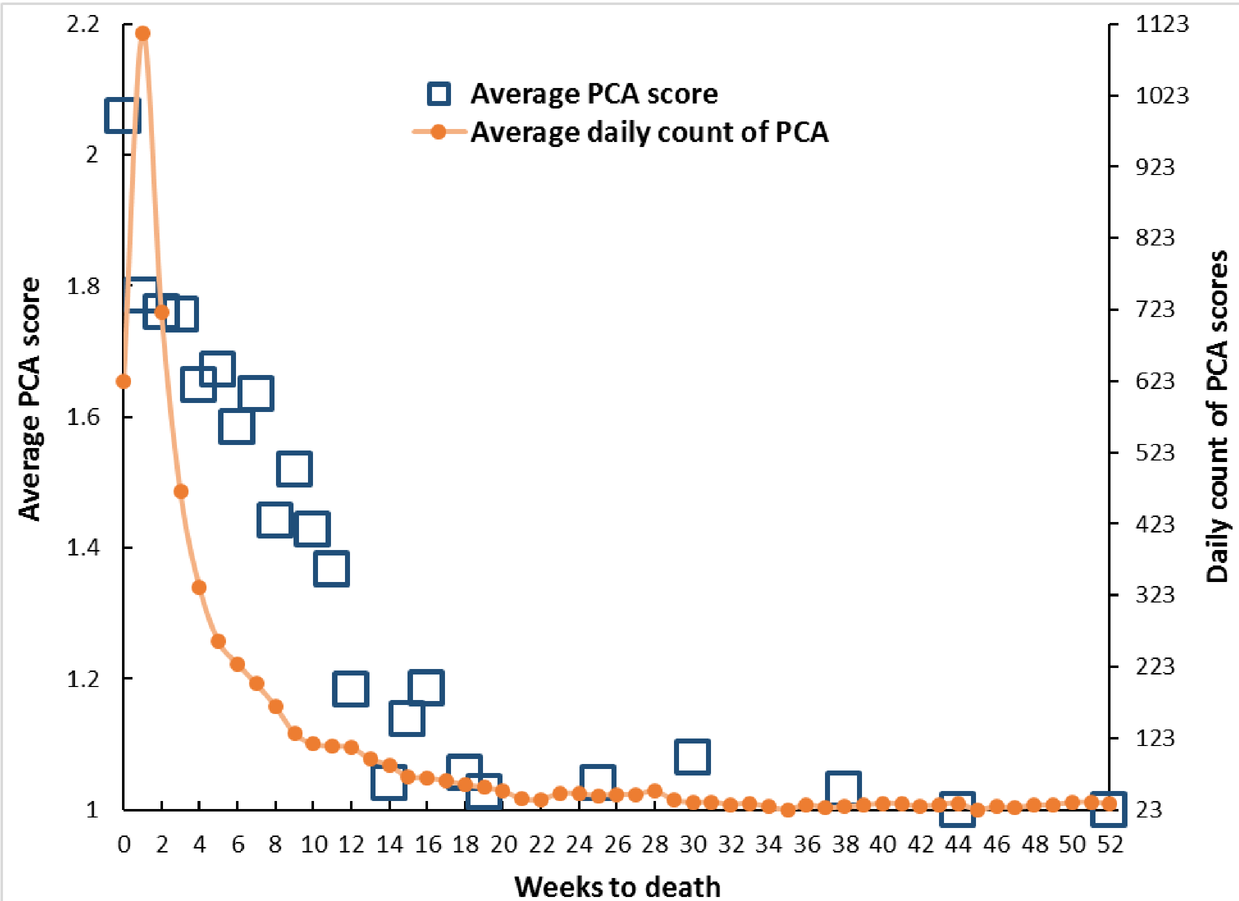

Fig. 2: Change in average PCA score and the number of weeks prior to death (n = 44,365)
The daily count of PCA is equivalent to occupied beds, due to double counting between the three data sets the trend is more a relative measure of occupied beds, i.e. bed occupancy in the dying peaks sharply in the last week of life.

The time trajectory in average PCA score prior to death for the smaller ICU data set is more gradual and only declines to an average of 1.0 beyond three years prior to death. The profile is also dominated by high average scores between 6 to 25 days prior to death, when the bulk of time in ICU would appear to occur (See Fig. A3). By implication persons who spend time in ICU have a poorer health state as measured by population average PCA score over an extended period prior to ICU admission, however, PCA score *per se* for individuals is not predictive of ICU admission. Those who are admitted to ICU have a wide range of PCA scores prior to ICU, but typically show a +1.0 change in PCA score between biochemistry conducted just before ICU and the first biochemistry after admission to ICU (data not shown). Factors other than the PCA score, such as liver function, comorbidity and physiology scores appear more important predictors of the need for ICU [6], although rapid deterioration in health state is implied by the higher PCA score soon after ICU admission.

Figs. 3a and 3b illustrates the more complex individual trends which lie behind the collective population trend seen in Fig. 2. In Fig. 3a, the male has repeated contacts and admissions at the hospital over a two-year period. His initial PCA score is above zero indicating poor biochemical balance. There are periods of acute exacerbation, with a final rapid and pronounced increase in the PCA scores (involving admission to intensive care) prior to death, with pneumocystosis as the primary diagnosis. In Fig. 3b, a woman with cancer has repeated visits/admissions, spends time in intensive care and finally recovers with the PCA score eventually returning to -1.0. Interestingly the rudiments of a weekly cycle in health can be discerned in both figures which leads to an element of apparently high volatility in the daily PCA scores (see also Fig. A1 for examples of day-of-week changes in the PCA score).

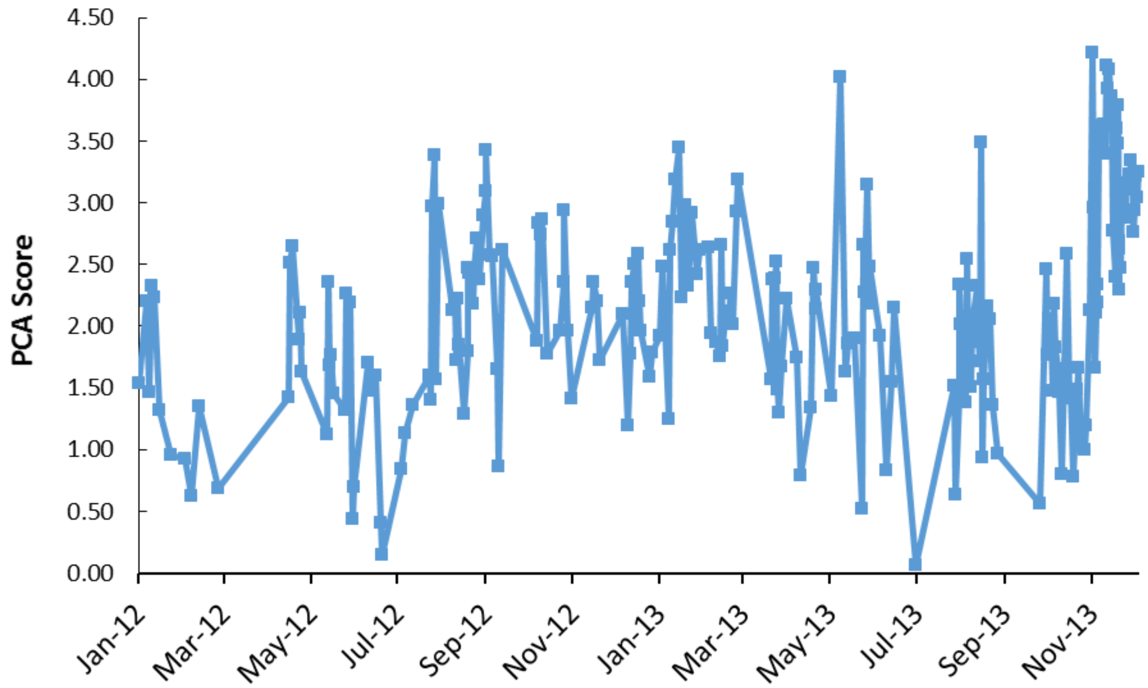

Fig. 3a. PCA score over time for a male aged between 50 and 60 years who eventually dies

Large gaps between data points indicate periods between consecutive hospital attendance/admission.

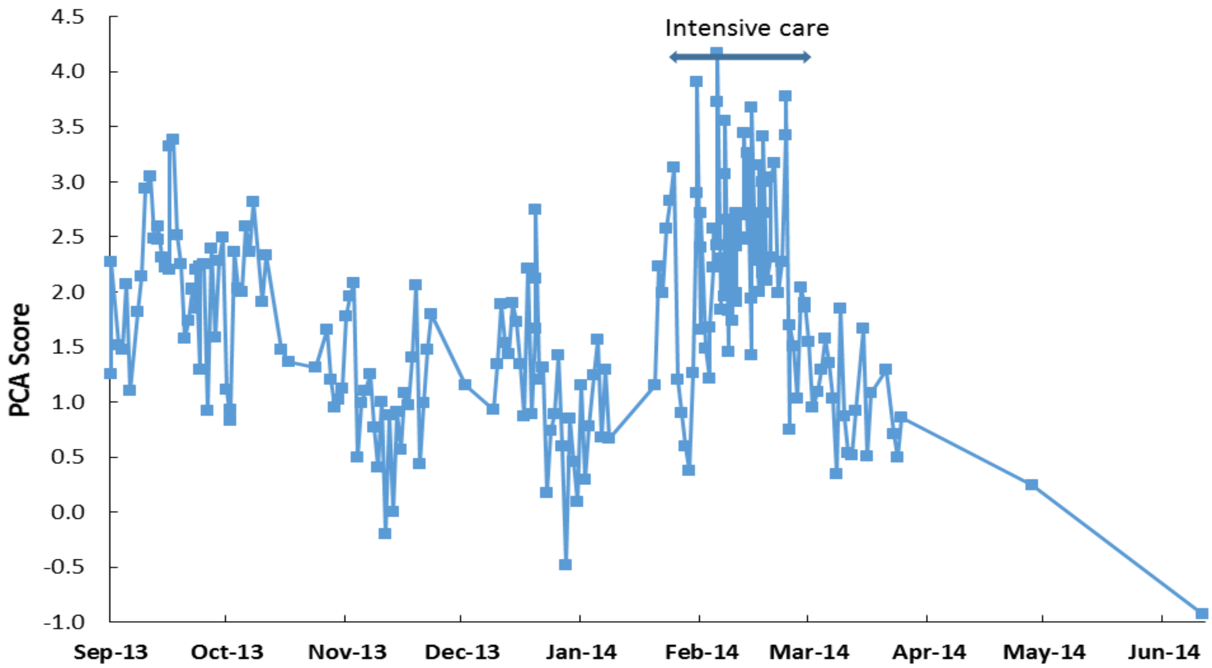

Fig. 3b. PCA score over time for a woman aged between 60 and 70 years who recovers after treatment

The final two data points come from follow-up visits to confirm the efficacy of treatment

In terms of potential seasonal effects, analysis reveals that there is no evidence for a seasonal effect upon the PCA score (Fig. A4), however, behavior of the 28 day running average PCA score over time suggests that it may be detecting as yet unexplained changes in population health status (possibly infectious), a possibility which requires further exploration. In this respect it should be noted that up to the present the vast quantities of pathology test results collected around the world have not been harnessed to their full potential, and that application into epidemiological studies is long overdue.

Given that higher PCA score has been shown to be associated with death, and has been shown to be highest in the demonstrably sickest patients in the hospital, i.e. on ICU, it is possible to investigate the detail of any day-of-week effects, with a higher average score potentially indicating a 'sicker' patient cohort.

3.1.2 Day-of-week patterns

Figs 4a and 4b show the day-of-week profile in the average PCA score for a cohort of patients who have all spent time in the intensive care unit. Fig. 4a shows the day of the week profile for average PCA scores during the time spent in the intensive care unit, while Fig. 4b expands this to include any previous and subsequent attendances/admissions for these persons over a two-year period. The intensive care unit was chosen because there are no day-of-week staffing issues, while the bigger picture for these individuals is used to illustrate common behaviour outside of the intensive care unit. Both figures show a clear day of the week variation in PCA score, being highest at the weekend and lowest around Wednesday.

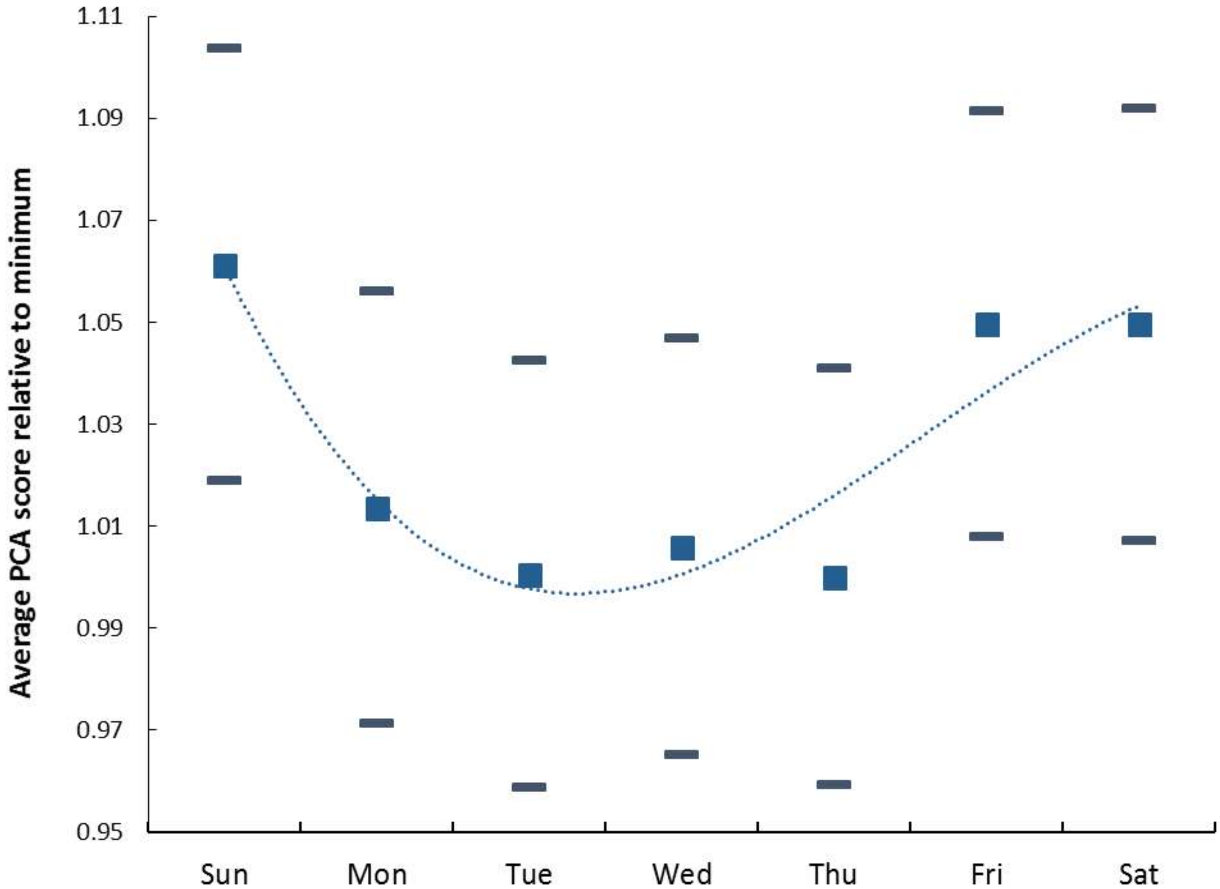
Average PCA score relative to minimum
1.11
1.09
1.07
1.05
1.03
1.01
0.99
0.97
0.95
Sun
Mon
Tue
Wed
Thu
Fri
Sat

Fig. 4a. Day-of-week effects upon the average PCA score for patients in the intensive care unit

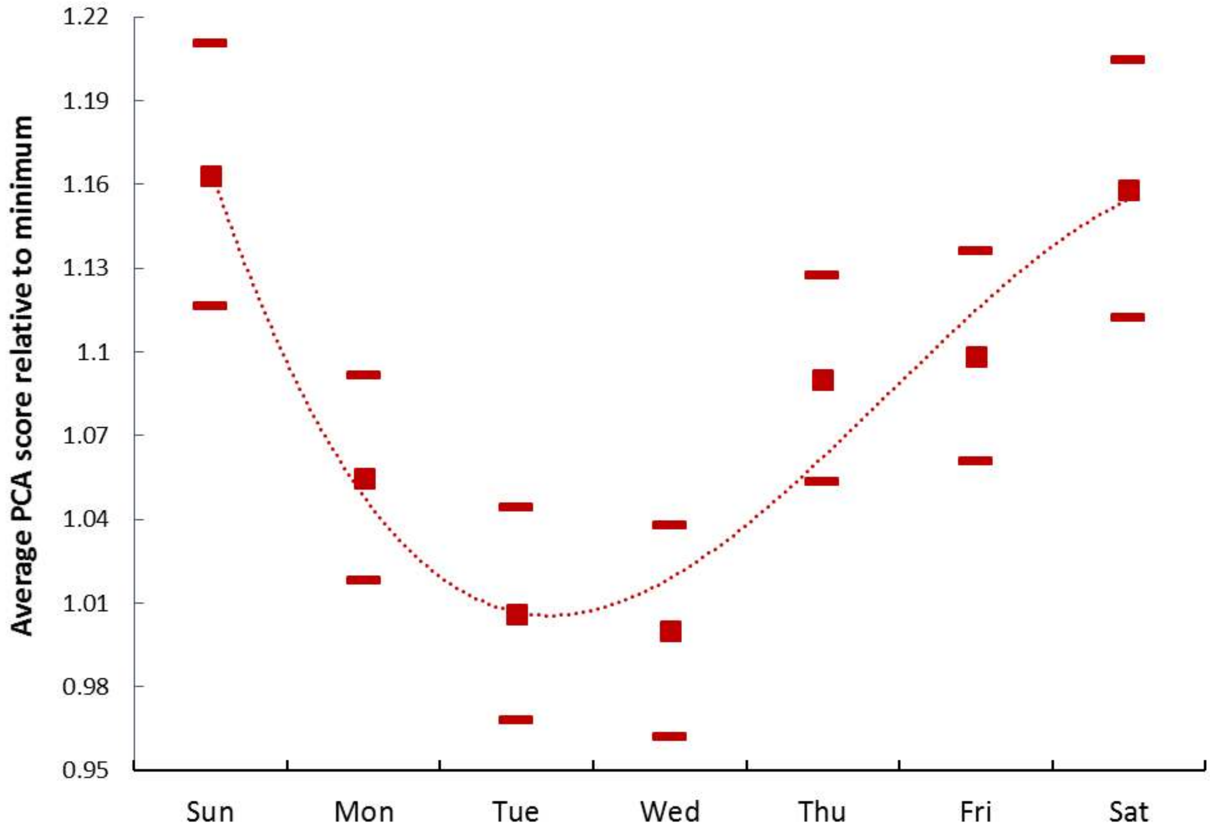

Fig. 4b. Day-of-week effects upon the average PCA score for patients who were admitted to ICU along with attendances/admissions for these persons previous to and after ICU admission/discharge

Fig. 5 shows the average PCA score by day-of-week for those patients who died in hospital (not necessarily in the ICU), and those who were still alive (all three data sets). The PCA score is calculated across all patient contacts during the study period, with alive/dead based on the status at final contact in the study period. The error bars are not shown in this figure since they overlap, i.e. given the sample size there is no statistically significant difference between the two groups. The number of test results in the 'died' group is significantly lower than the 'alive' group, and hence the trend line appears more volatile. This shows that in both the people who were still alive at the end of the study or those who died there is a clear day of the week variation in PCA score, being highest at the weekend and lowest around Wednesday.

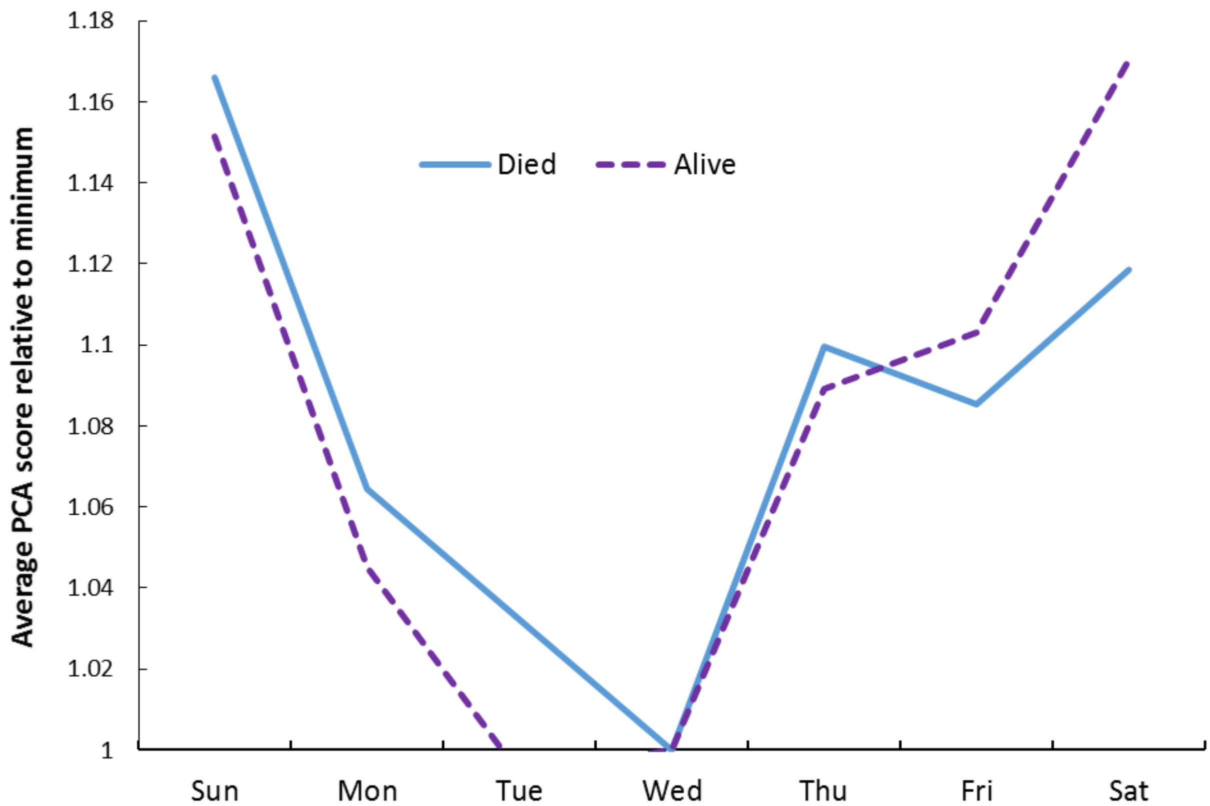

Fig. 5: Weekday trend in average PCA score for patients who spent time in intensive care and who eventually died in hospital or were alive at discharge
Includes PCA score for any outpatient (n = 240), A+E (n = 2082), intensive care (n = 8936) or other inpatient stay (n = 15,505) for each patient over the entire study period.

Fig. 6 (a composite from all three data sets) explores the possibility that different patient groups may experience different weekday profiles for the average PCA score. On this occasion the absolute difference in the PCA score has been displayed in Fig. 6 rather than the percentage change, since the percentage change can be unduly magnified in those situations where the PCA score is close to zero. As can be seen the profile is most pronounced for stroke rehabilitation, acute cardiac care and general cardiology down to intensive care as the least pronounced. Both general surgery and trauma and orthopaedics show statistically insignificant changes which confirms the observation that death in persons with a low PCA score is usually caused by sudden organ failure, i.e. the blood biochemistry has had no time to change away from the basal ‘healthy’ level.

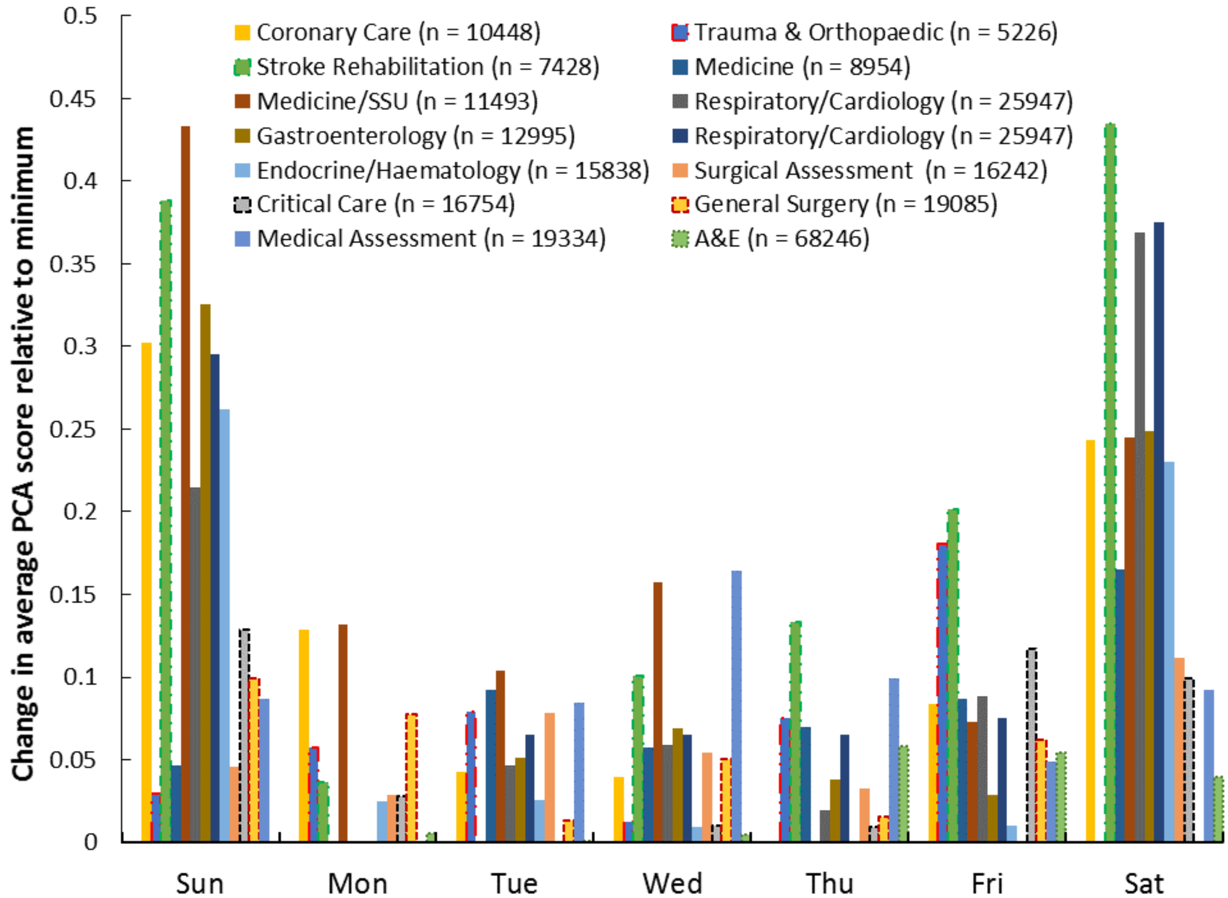

Fig. 6. Weekday difference in average PCA score (relative to minimum) for patients on different wards

Fig. 7 therefore explores the effect of age on day-of-week profiles. As can be seen in Fig. 7 the 'weekend' effect is strongest for the age band 51-70, and diminishes for ages above and below. The day-of-week profile gradually strengthens from slightly weekend biased at 31-40 through to a stronger profile at 41-50. Beyond 51-70 the profile once again weakens, and may even slightly invert above age 80 in those patients who are approaching death, i.e. higher in mid-week (see Fig. 8).

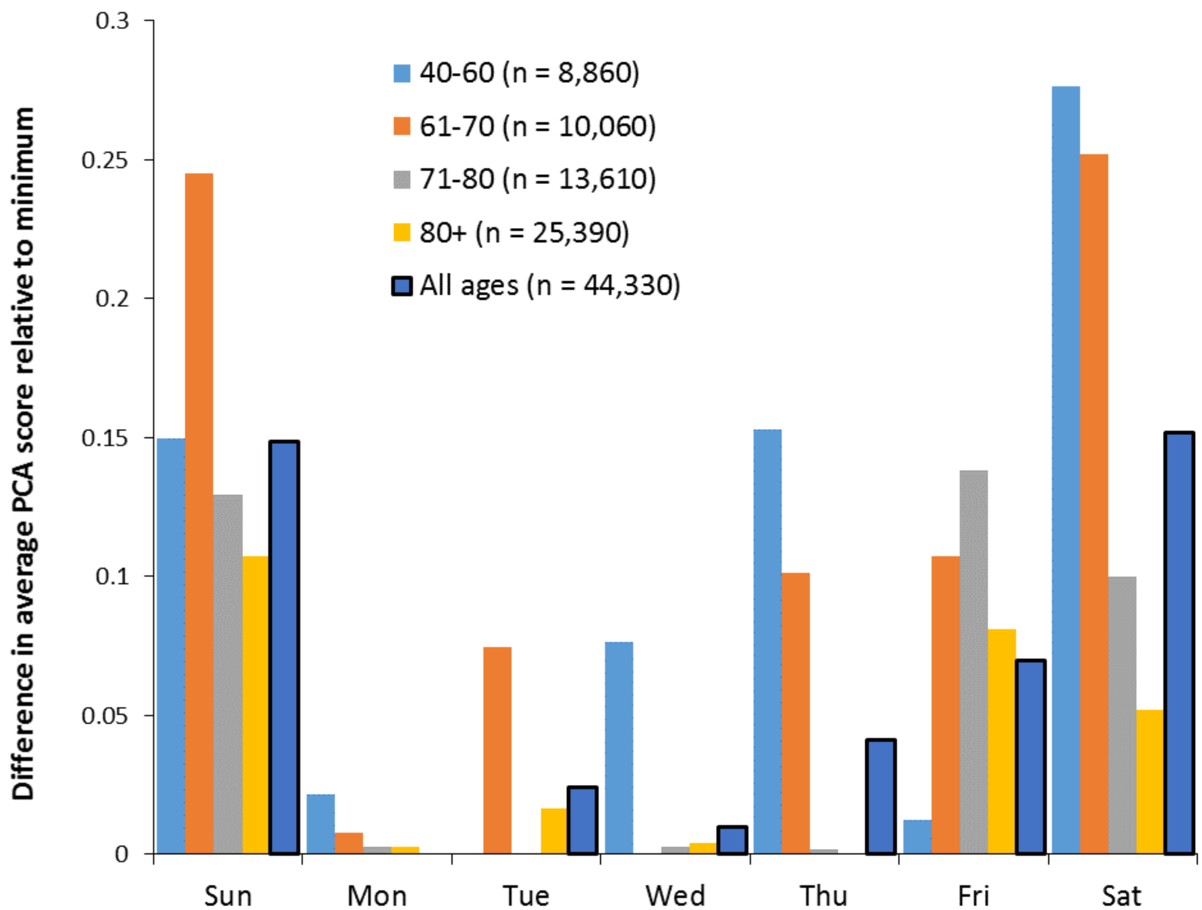

Fig. 7. Effect of age on weekday differences in average PCA score

Finally, Fig. 8 explores the effect of time to death on the strength of the weekend effect. In this figure time to death was calculated for every occurrence of biochemistry tests. The strength of the weekend effect was calculated as the average PCA score for weekends (Saturday and Sunday), divided by the average PCA score for midweek (Tuesday to Thursday). A score of 1.0 therefore is equivalent to no weekend effect, >1 a weekend effect, and <1 indicates higher PCA scores in midweek rather than weekend, i.e. an inverted profile. Fig. 8 requires some explanation. The majority of biochemistry tests occur close to death and in order to avoid small number effects, the cumulative PCA score for each day of the week was calculated from death backward. Scores are therefore cumulative (moving away from death), and illustrative of the fact that the strength of the weekend effect increases further away from death. Closer to death it weakens, flattens and then inverts. Exactly when the average strength of the weekend effect flattens cannot be discerned in these cumulative charts, however, it will be shifted to the left of the apparent point in the cumulative chart. Larger national samples will be required to clarify the exact nature of these effects, and if they are also condition specific.

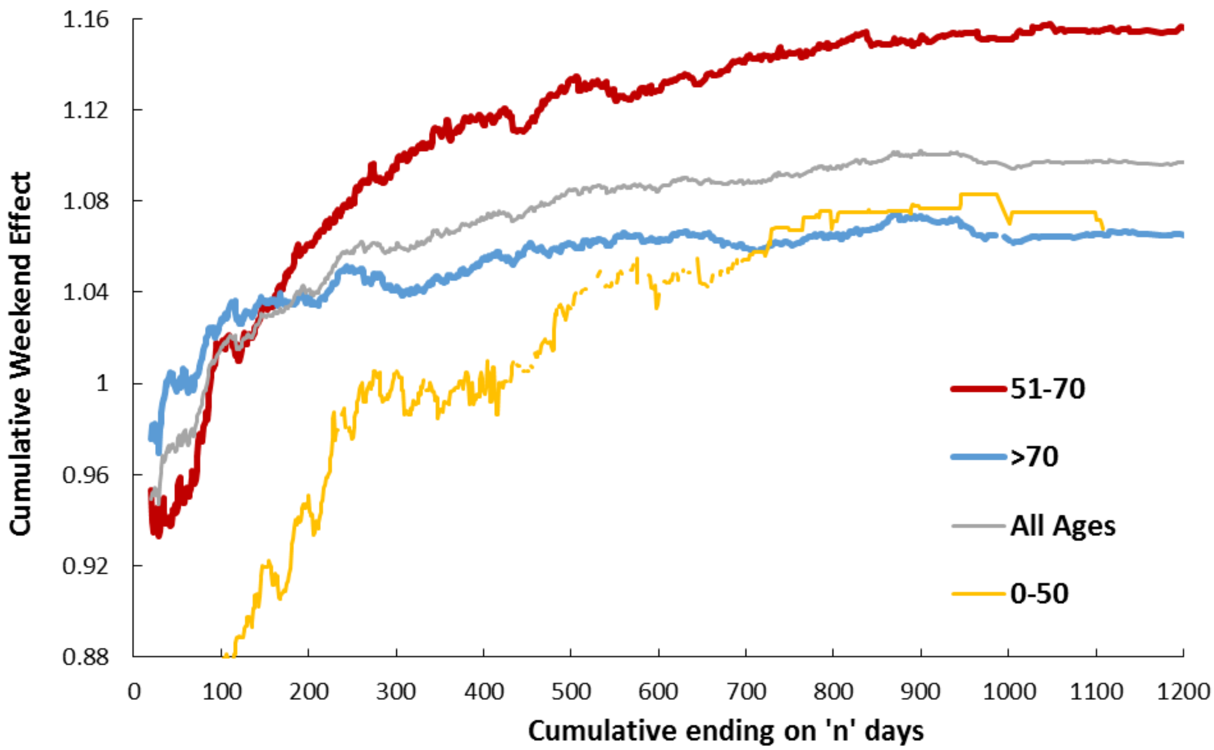

Fig. 8. Age and time to death and strength of the weekend effect

3.2 Discussion

3.2.1 History behind the study

This study was originally initiated to investigate if the PCA score could assist MKUH in the investigation of in-hospital deaths as measured by the Hospital Standardized Mortality Ratio (HSMR). MKUH already ranks in the best 10% of hospitals in England for HSMR, however, unexplained differences in HSMR between clinical divisions were of interest. It quickly became apparent that while the absolute value of the PCA score was not a direct predictor of death, at the level of the individual patient, a significant deterioration in the PCA score seemed associated with persons who were about to die. The project was then expanded to investigate death associated with 'weekend' admission, which was a highly topical issue at that time in England.

3.2.2 Insights from the literature

Both weekend and day-of-week effects upon hospital mortality are a well-documented phenomenon, with over 120 studies located in our literature search (available on request).

A wider search of the literature seems to point to the possibility that day-of-week effects upon human health and mortality may also occur. Acute cardiovascular disease has a distinct Monday peak for both admissions and in/out-of-hospital deaths, and also has seasonal and circadian patterns [7-8]. Age-specific effects have also been reported, and cardiovascular mortality in men aged <65 years is highest on Mondays and Saturdays [7]. Death from suicide shows day-of-week patterns [10]. In England and Wales from 1969 to 1972 deaths from myocardial infarction, cerebrovascular disease, other cardiac diseases and to a lesser extent, bronchitis and pneumonia, all showed a Monday peak, while influenza and pneumonia showed a Saturday peak [11]. The occurrence of stroke is day-of-week specific, however this depends on the type of stroke; where cerebral infarction is more prevalent on a Monday and less so on Thursday/Friday, while cerebral haemorrhage or subarachnoid haemorrhage show no day of week variation [12].

Other factors can affect day of death, and patients on different dialysis schedules experience different weekday patterns of cardiovascular and non-cardiovascular death [13]. A Canadian study of deaths from 1974 to 1994 noted day-of-week effects upon all-cause mortality, with highest average deaths on a Saturday and lowest on Thursday. This profile was more exaggerated for motor vehicle deaths with a minimum between Monday to Wednesday, and a distinct day-of-week cycle on the other days peaking at Saturday (40% higher than Wednesday). Suicides showed a less pronounced cycle with a minimum on Thursday, which was 8% less than the maximum on Sunday [14].

Further day-of-week effects have been observed in the stock market volatility and returns [15-16]. Worker productivity appears to show day-of-week effects [17], as does job satisfaction and feelings of personal well-being [18-19]. Mood, vitality and sickness symptoms also show day-of-week effects [20]. College students show a weekend peak in smoking frequency [21]. The ability to assimilate and retain new information in college students peaks on Wednesday [22]. This limited selection should be sufficient to point to the possibility of day-of-week effects in hospital mortality arising from a fundamental human weekly cycle in both mental and physical health. It is of interest to note that atmospheric temperature also follows a weekly cycle which seemingly arises from the day-of-week patterns in human activity [23].

There have been relatively few studies on the day-of-week cycles in blood biochemistry. One study conducted in 1935 demonstrated that the levels of blood constituents varied considerably from day to day, and that the degree of variability appeared to correlate with the personality trait of emotional stability [24]. It would appear that the PCA score is a way of summarising some of this natural variability.

Hence, while a fundamental week-day cycle in human health and wellbeing appears to exist the issue of higher mortality associated with weekend admission appears complicated by a range of factors. The seminal review by Becker published in 2008 identified the following issues relating to studies in this area [3]. Firstly, the potential for selection bias for patients admitted on the weekend. This author cited an example of one study which showed that conditions having the greatest decline in weekend admission also showed the highest apparent weekend mortality. Secondly, aggregation of conditions can mask underlying differences between conditions, an issue relevant to the larger all-condition studies. Next, few studies have explored the specific pathways by which the weekend effect may occur, and finally solutions to the problem must be tailored to the exact cause(s).

Based on the 120 studies identified in our literature search the following general observations are relevant which demonstrate that the observed day-of-week effects in inpatient mortality is indeed a composite of different causes. Selected studies from the 120 have been cited.

Irrespective of setting or patient group the profile of inpatient mortality is clearly a day of week (admission) profile rather than a simple ‘weekend effect’ [2,25-27]. This also applies to emergency and elective general surgical patients [26-27], and also to delivery and obstetric outcomes, except that different shaped weekday profiles applied to different conditions [28]. Somewhat cryptically, those already in hospital are seemingly less likely to die on a weekend, with a slight peak around Monday to Tuesday [29]. A section in the discussion is devoted to explaining this apparent contradiction in the light of the curious behaviour of the PCA score as the point of death draws near.

However, for a set of specific conditions access to resources (mainly staff) leads to higher weekend mortality. This effect is generally higher in smaller hospitals [30-31], is associated with a lower standard of documentation [32], and is also higher in out-of-hours admissions [36-37]. Higher rates of 11 hospital-acquired conditions for weekend admission have been documented [37], as has lower access to interventions/procedures on a weekend [38-41], and lower access to multi-disciplinary care [42]. The effect seemingly reduces over time as resource inequalities are remedied [43]. For example, reduced for COPD after the introduction of a 24/7 medical assessment unit [44]. The weekend effect is absent in well-resourced Level 1 trauma centers [45], other specialist units [48-49], intensive care units [49-51], in a specialized neurosciences intensive care unit (where no out-of-hours effects were also observed) [49], or where emergency surgery is routinely available, i.e. laparoscopic appendectomy [52], and only for a set of specific conditions [29,53-54].

For some conditions, such as meningococcal disease, there is no difference between day-of-week for in-hospital death and for those who are never admitted [53]. However, certain groups of patients are 'sicker' on the weekends, i.e. selection bias. In this respect numerous studies have confirmed a drop in admissions over the weekend such as: all admissions -41% [54] hip fracture -2.4% [55], general stroke -21% [56], acute ischemic stroke -3.8% [46], urgent surgical interventions -23% [57], urgent pediatric surgery -14% [58], lower extremity ischemia -54% [59], leukaemia -50% [60], metastatic prostate cancer -50% [61], acute myocardial infarction -4% [62]. This is not universal and some admissions increase on the weekend such as non-ST-segment elevation acute coronary syndrome +2.7% [62]. Leukaemia and metastatic cancer patients presenting on the weekend are 'sicker' than their weekday equivalent [59-60], and biochemistry-based risk scores in medical patients are higher on the weekend [63]. Various specialised person-based risk scores for particular conditions are higher at the weekend [44,45,61,64], and in one study of medical admissions such adjustment reduced the apparent value of the weekend effect by 50% [63]. Medical patients admitted on the weekend have a higher incidence of neurological conditions and less gastrointestinal conditions [64]. The proportion of persons admitted to intensive care is higher on the weekend [34], with ICU admission generally omitted as a risk factor in most models. Intracerebral haemorrhage score (ICH) was higher for weekend patients admitted to the ICU [66]. All-cause mortality in senile elderly men is higher on the weekend [67]. Stroke admissions on the weekend are more likely to require thrombolytics or tissue plasminogen activator [65,68]. Upper gastrointestinal bleeding patients admitted on the weekend had higher rates of shock, melaena, hematemesis and red blood cell transfusion [69-70], and higher death rates could not be fully explained by delay to endoscopy [39,71]. Peritonitis admissions are more complex on the weekend [47]. Patient safety indicator (PSI) events have similar incidence for weekend and week day admissions, however, when a PSI occurs for a weekend admission the risk of death is substantially higher [72] - either 'sicker' patients or staffing. Weekend effect is restricted to a particular set of conditions [73]. Higher acuity can be inferred from a US study where the weekend effect was highest in major teaching hospitals compared to non-teaching hospitals [73].

The study of Freemantle et al [2] demonstrated that risk of death for Sunday admission relative to Wednesday was condition specific with all-condition mortality (1.5-times), cardiovascular (1.2-times), and Oncology (1.29-times). A study on obstetric outcomes showed a progression to higher weekend admission for the most deprived, and a somewhat confusing range of day-of-week profiles depending on the condition being measured [28]. Studies at different locations (ethnic groups) can give conflicting results, and medical admissions in Kenya showed no weekend effect compared to most other Western studies [74].

The weekend effect can disappear as conditions are stratified by specific type. The magnitude of the difference between weekend and weekday is highly condition specific [75], hence all-cause studies which group many diagnoses into a limited number of groups may be inadvertently mixing dissimilar conditions. The weekend effect disappears when stroke admissions are stratified into ischaemic or haemorrhagic types, plus full adjustment for individual risk factors [12,76].

As can be seen the reasons for the weekend effect appear highly multifactorial and condition specific. The studies of nurse to patient ratios (including nurse education and qualifications), and their effect upon hospital mortality [77-79], appear to have led to the *de facto* conclusion that patients admitted on the weekend must therefore have higher mortality due to staffing alone. Dissonant studies such as the effect of day of onset for stroke [76,80], and a weekday cycle in intensive care mortality [81], appear to have not been generally referred to in the ensuing debate.

It is also apposite to remember that relevant factors may be overlooked. For example, in one study on death from sepsis in intensive care units there were no demonstrable weekend or night admission (from the ED) effects on mortality, however daily bed occupancy was associated with higher mortality [82], i.e. the issue may not be about staffing per se but about surges in busyness [83]. Busyness is known to be associated with many types of poor outcome in hospitals [84,85].

3.2.2 Have the mortality models contributed to the confusion?

To understand how the PCA score may shed light on the weekend effect we need to understand the limitations of the current methodologies. Firstly, both the hospital standardised mortality rate (HSMR) and the summary hospital mortality index (SHMI) are heavily reliant on the use of diagnosis as the fundamental basis for assessing supposed 'excess' mortality [86]. All known clinical models for predicting hospital mortality and death subsequent to discharge rely on a mix of vital signs, biochemistry test results, metabolic profiles, inflammatory markers and cognitive state (in the elderly) [1,87-95]. Addition of co-morbidity to one laboratory test-based method did not improve the model prediction [95], emphasizing that diagnosis *per se* is of limited value. Since these are not routinely available in the NHS, modellers have resorted to readily available administrative data as a proxy for the more accurate clinical variables.

In any attempt to model, the use of proxies is a decidedly questionable basis for the production of an adequate model. For example, at the Milton Keynes University hospital (MKUH) the instigation of clinical audit by the Mortality Review Group of supposed instances of excess mortality as measured by HSMR and SHMI has only ever uncovered false positive flags. Clearly the models are not infallible. A clue to this potential unreliability lies in a comparative study on day-of-week profiles between hospitals in the UK, US, Australia and the Netherlands relating to emergency and elective surgical admissions [27]. This was a large study conducted over four years. Australian hospitals showed no day-of-week effects for deaths up to 30-days post emergency discharge, but did show a profile for 7-day mortality. While most hospitals displayed a roughly similar Saturday and Sunday effect for emergency surgery at 30-days post discharge, Dutch hospitals showed an apparent very large Saturday effect for maximum elective mortality. Minimum elective mortality appeared to occur on Tuesday, except for Friday in the US, while minimum emergency mortality occurred around Tuesday or Wednesday except for the Netherlands on a Friday [27]. So-called process differences are unlikely to explain such seemingly anomalous profiles.

Finally, is there any evidence that the weekend effect for admission to hospital may in some instances be an artefact? In a Japanese study of mortality following stroke, the weekend effect, based on day of admission, disappeared when mortality was re-calculated using day of onset [80]. A US study of patients admitted to the intensive care unit (ICU), where staffing is can reasonably be assumed not to be an issue, showed a 9% higher disk of death for patients admitted to the ICU on the weekend compared to mid-week. However, risk of death was also 8% higher for admission on a Monday or Friday, i.e. a day-of-week cycle rather than a simple weekend effect. Length of stay was also 4% higher for weekend or Friday admission compared to mid-week. The authors concluded that the weekend effect was most likely to be due to unmeasured severity of illness rather than differences in quality of care [81]. In an Australian study it was observed that stillbirths, low birth weight and neonatal mortality were all higher for weekend born babies – an effect which was concluded to be unrelated to variation in the quality of care over the weekend [96]. These are examples of human health being poorer at the weekend, and if true, would act as a confounder for weekend admissions.

It is of interest that the UK study [2] steered clear in its discussion on the wider day-of-the-week literature. This paper was also careful to avoid discussion of studies showing that crude adjustment based on routine data leads to over-estimation of the weekend effect. Hence numerous studies (discussed above) showing a reduction in the weekend effect after the inclusion of patient-specific risk factors. It has been repeatedly noted in the literature that risk of death in the elderly is far higher for persons with delirium and other cognitive function deficits [97], and these and other person-specific factors such as number of prescribed drugs [98-99] are omitted in the majority of the larger all-cause studies using simple administrative data, i.e. they simply have insufficient relevant information to accurately quantify any weekend effect. A large study of mortality after cardiac surgery (where staffing issues are not a problem) noted that 95.75% of the variation in in-hospital mortality was due to patient specific risk as measured by the EuroSCORE model [100]. However, in support of a probable link with weekend staffing, is the observation that adverse events are more common in those who die in hospital [101] – although the effect may be due to poor care pathways than number of staff *per se*. Another study on emergency general surgery showed that resources were involved with lowest overall mortality in UK Trusts with highest levels of medical and nursing staff, and those with highest provision of operating theatres and critical care beds [25]. As in other studies a distinct day-of-week profile was observed with a minimum on Wednesday.

Also it is surprising to note that many studies on this topic establish that the 'weekend' effect is actually a day-of-week pattern, with a minimum in mid-week and a maximum on Sunday, or variations on this theme, [102] with patterns seemingly shifted either forward or backward by one or more days. Having explored the complex issues behind the 'weekend effect' and how it may or may not link to staffing, the issue of how the PCA score could shed light must be addressed.

There are two fundamental approaches to measuring the day-of-week effects on the PCA score. The first would involve single measurement of PCA score from individuals based on random day-of-week sampling. Patients attending A+E but not then admitted are an example of this approach. As can be seen from Fig. 1 this approach suffers from the wide variability in PCA scores between individuals. The second approach is to follow single individuals with multiple samples taken on different days, which is illustrated in Fig. 3. On this occasion the variation in PCA score over time is far less that the variation between individuals. To gain the benefit of this approach this study has used linear interpolation to replace missing values so as to generate a long time series for all patients with a prolific biochemistry history. This is then supplemented by random scores from other patients whenever all 12 tests were present.

3.2.3 Age and the PCA score

Our unpublished studies on the complex nature of the biochemical issues reflected in the composite PCA score are most apparent in the effect of age. The following preliminary observations, are apposite. Firstly, on the day of birth the average score starts at around -3.0, and then steadily climbs to around +1.0 at day 45 of life. The score then reaches another minimum around day 160 followed by various shifts up and down through to the first birthday. Beyond the first birthday the average score then progressively declines to another minimum of around -2.0 between the ages of 16 to 18, and thereafter shows a slow increase with age, interspersed with periods of higher score during illness, and a sudden jump to higher values in the months or days preceding death. Interestingly the distribution of individual PCA scores at each age is skewed, but the skewness changes with age. Clearly the PCA score is reflecting complex developmental changes along with complex distributions of the score for individuals, which is also reflected in the subtle day-of-week changes observed in this study.

In Fig. 7 the following data is not shown, but is illustrative of the complex relationships with age. No standard weekday profile can be discerned in the first year of life due to the complex movements in the average score discussed above. For the age band 1-10 there is a strong weekday profile roughly similar in magnitude to the age band 51-70 shown in Fig. 7. The weekday profile in the teenage years appears to be inverted with lowest average PCA score on the weekends – which may partly explain the weekend behaviour of teenagers in general. The error bars for age 21-30 all overlap, and there are probably no day-of-week effects for this group (data not shown). Day to day changes in human biochemistry and health are seemingly far more complex than has hitherto been appreciated.

3.2.4 The PCA score and biochemical imbalance

This study has firstly demonstrated that the PCA score (as a measure of biochemical imbalance) is indeed a measure (albeit a complex one) of frailty and mortality, and can therefore be usefully extended to examine the issues regarding the weekend effect. Hence Table 2 demonstrated a logical gradient in average PCA scores between different hospital departments which highest average in the ICU and lowest in the A+E among those who were not admitted, and in various outpatient departments. Fig. 1 demonstrated age dependent changes in PCA score for those who were not admitted, with generally higher PCA scores in those who died. Fig. 2 illustrated the fact that the population average PCA score tends to rapidly increase at around 20 weeks prior to death, and that the average PCA score on the day of death is generally the highest. Finally, Fig. 3a and b showed a time profile for an individual who eventually died just after a stay in ICU and one who showed full recovery. Potential day-of-week effects could be discerned.

Having established the credibility of the PCA score as a measure of declining health and immanence to death, Fig.s 4a and 4b illustrated that the day-of-week effect in the ICU was slightly lower than for the same patients both within and outside of the ICU. Given that a stay in the ICU represents a period of the highest PCA score for an individual, and that these individuals are being kept alive by active intervention, the lower week day gradient is probably constrained by the fact that the PCA score for that individual is already high. However, Fig. 4a in particular has clearly established that in an inpatient environment where weekend staffing is not an issue there is still a weekday effect inherent in human health.

Fig. 5 demonstrated little difference between those who die and those still alive regarding day-of-week effects. The same profile observed in many studies applies with highest average score on weekends and a minimum around Wednesday. Differences between hospital departments were then illustrated in Fig. 6 with the lowest day-of-week cycle seen for those who are closest to being healthy, i.e. orthopaedics, surgery, and the emergency department.

The effect of age reveals more complex patterns in the day-of-week cycle with maximum weekend difference seen in those aged 61-70. Potential inversion in the week day profile for those aged over 80 and the ‘teenage’ effect prompted the final evaluation of the shape of the day-of-week cycle as a function of both age and time to ultimate in-hospital death. Complex age and time-to-death profiles were revealed and the weekend bias in the day-of-week profile in the average PCA score seems to diminish at around three years prior to death, reaches a flat profile and then seemingly inverts to higher mid-week scores (similar to the teenager effect) at times very close to death.

Clearly the PCA score is detecting highly nuanced changes in the day-of-week profile of biochemistry test results which has hitherto not been appreciated. Indeed, how doctors interpret biochemical scores may need to be re-evaluated in the light of these findings. It is implied that how age standardization is applied in the base models of many studies may contain flaws affecting the perceived weekend effect as the living and the dying (according to their age) respond differently to time. A seemingly complex series of confounding effects can be anticipated in studies seeking to characterise the weekend effect in the absence of a knowledge of the importance of biochemical issues.

3.2.5 Why do in-hospital deaths peak in mid-week?

There are a number of apparent contradictions between higher mortality for those admitted on the weekend, slightly higher in-hospital deaths during mid-week, 30 and the apparent behavior of the PCA score with the approach of death. The following observations are an attempt to reconcile these apparent contradictions with the observed behavior of the PCA score close to death.

Firstly, many of those who die in-hospital, and within 30 days of discharge have a cancer as their recorded cause of death (as per mortality coding rules), but will have something like pneumonia recorded as their reason for admission (morbidity coding rules). As a result, the pneumonia group usually shows up as the largest cause of death at the MKUH Mortality Review meetings. See Fig. A5 for an example of persons whose cause of death is lung cancer, yet the reason for admission. i.e. their required management, is reported on 65% of occasions as something other than lung cancer.

Second observation, in the literature it is noted that in-hospital day of death has a slight peak toward mid-week [30], while death associated with day of admission has an apparent contradictory weekend peak.

Curiously, the day-of-week profile of the PCA score (blood biochemistry) inverts as the person gets closer to death, i.e. the PCA score on the weekend of admission will show a tendency to a weekend peak, while it will show a midweek peak on the day of death - as per the conundrum posed above.

In addition, the literature is reasonably consistent that cancer patients admitted on the weekend are more complex than their weekday equivalent [60-61].

Lastly, the higher weekend PCA score for those who are discharged alive could potentially explain the higher re-admission rates observed in those discharged on the weekend [103], i.e. they are sicker.

Hence both this study on the PCA score and the wider literature agree that the seeming higher death for weekend admissions is probably around 50% lower that its seeming value due to the inability of current mortality models to adjust for the subtleties associated with the real cause of the admission and the approach of death.

3.2.6 Implications to the NHS

It is vitally important to remember that over 90% of all deaths following admission to hospital are medical in nature (at MKUH 4% are orthopaedic and 6% are surgical). While elective surgical deaths may be higher on the weekend, the numbers are so small that unfocussed attempts to address any problem would have a poor cost benefit ratio. It would simply be easier to not conduct elective surgery on the weekend.

Any issues with trauma weekend admissions are simply addressed via well-staffed regional trauma centres dealing with the highest risk patients [45]. The same applies for various cardiovascular and digestive conditions [46-51].

Birth is one of the few genuinely 24/7 activities and resources have been matched to this reality since before the NHS was established. Unrestricted immigration into the UK of mainly younger people, together with a serious issue regarding bed availability, coupled with fewer trained midwives has led to a somewhat intractable situation [104-106]. Day-of-week deaths for birth related conditions likewise show a confusing variety of profiles suggesting that a specific plan of action (which may or may not involve doctors) is required. The PCA score associated with obstetrics/maternity in Table 2 is surprisingly high (given the relatively young age of expectant mothers) suggesting a weekend effect is possible due to biochemical factors. A far larger national study would be required to resolve these issues.

3.2.7 Primary cause of death

With reference to the discussion above, a massive 33% (1271/3882) of all deaths at MKUH have cancer as the primary cause of death (as described on the death certificate), which lies masked behind a diverse range of diagnoses relating to the condition requiring management at last admission. This reality will be totally ignored by all current models predicting so-called weekend mortality. It is also known that cancer patients admitted on the weekend are ‘sicker’ than weekday admissions. It is highly unlikely that poor medical care is contributing to these deaths since MKUH consistently lies in the lowest 20% of hospitals for in-hospital deaths as measured by HSMR.

At MKUH the next highest reported cause of death are various respiratory conditions (mainly pneumonias and COPD) accounting for 22% of all deaths (844/3882). Medical consultants make the observation that pneumonia is an ‘end of life’ disease, i.e. it is the manifestation of declining health and immune function. A national programme to focus on the management of pneumonias may be of benefit, but at the same time may fail to prevent an appreciable number of persons from somewhat ultimate and certain decease.

The issues appear far more complex than at first thought, and the plans (and assumed reduction in mortality) to introduce 7-day (doctor) working in England based on this assumption may be flawed.

3.2.8 Limitations of the study

The limitations of this study are that it does not investigate circadian or gender effects. The study Is limited to the frequency of testing dictated by patients in various departments at a typical general hospital and is mainly for unscheduled attendances/admissions. This study needs to be complemented by studies on ‘healthy’ persons with samples taken at the same time each day.

3.2.9 Further research

Effects during first year of life or oldest ages will require a national data set to fully elucidate. Long-term studies are required to elucidate if persons with a low PCA score live longer than their higher PCA score counterparts. The role of specific diseases and cancer types on the PCA score requires further investigation. The potential for the PCA score to detect events of public health significance needs to be further explored. Why the apparent variation in the PCA score reaches a minimum around age 10 requires investigation.

4. CONCLUSION

The very fact that other studies have used biochemical scores to develop risk of death models [1,87-95], confirms the assertion that what is being observed is not exclusively due to poor care but rather is partly due to a day-of-week cycle in patient acuity. This study has not proved this link per se but has inferred that it is highly likely. Based on the literature our best estimate is that around half of the so-called weekend effect is probably due to biochemical and specific patient-risk factors, which will considerably affect any return on investment calculations relating to proposed 7-day working in the NHS in England. This is probably an underestimate given the large numbers of hospital deaths which are actually cancer related as the primary cause of death.

This is not an argument to retain lower staffing levels on the weekend (although well-staffed regional centres make more sense for specific conditions), but rather that anticipated reductions in in-hospital mortality may be significantly less than otherwise anticipated. Indeed, some are already beginning to question if the cost of the implied extra staff may outweigh the anticipated benefits [107], and a net benefit approach is required [108]. Other research suggests that the high occupancy so common among UK hospitals [84,85], may also act as a mitigating factor in the ability to make the reductions in deaths, which the studies on weekend mortality seem to imply are possible – within the context that poor staffing ratios will always lead to poor outcomes [109]. As suggested in the seminal review by Becker [22], tailor the solutions exactly to the real cause(s) of the problem(s), rather than indiscriminately throwing doctors at a perceived, and ill-defined problem.

The study of Concha et al [110] is entirely relevant in that they demonstrated that only 16 of 430 diagnosis groups (accounting for 40% of deaths) had a significantly higher weekend effect. As mentioned earlier, both experience and recent research [111-121] shows that current HSMR and SHMI models are poorly suited to pointing anyone in the right direction, and they miss the subtleties associated between the reasons for admission (medical management of a presenting condition) versus the genuine underlying cause of death.

The inversion in the PCA score toward the last days of life appears to explain the apparent conundrum as to why in-hospital deaths appear to slightly peak in mid-week, while weekend admission seems linked with higher death.

CONSENT

No patient consent was required for this retrospective study which did not involve any patient contact or intervention. No patient identifiable data is contained in this study.

ETHICAL APPROVAL

Ethical approval was not required for this retrospective study, which is for the purpose of epidemiological study. The need for ethical approval was checked using the on-line tool provided by the NHS Health Research Authority (England), see http://www.hra-decisiontools.org.uk/ethics/. Internal approval for the study and study oversight was given by the Hospital Medical Director. The data used in this study is not available outside of MKUH.

REFERENCES

1. Cohen A, Milot E, Li Q, et al (2015) Detection of a novel, integrative aging process suggests complex physiological integration. PLOS ONE 2015;10(3):e0116489.
2. Freemantle N, Ray D, McNulty D, et al. Increased mortality associated with weekend hospital admission: a case for expanded seven day services? BMJ 2015;351:h4596.
3. Becker D. Weekend hospitalization and mortality: a critical review. Expert Rev Pharmacoeconomics Outcomes Res 2008;8(1): 23-6.
4. Jones R. Does hospital bed demand depend more on death than demography? Brit J Healthc Manage 2011;17(5):190-7.
5. Jones R. End of life care and volatility in costs. Brit J Healthc Manage 2012;18(7):374-81.
6. Delgado M, Liu V, Pines J, et al. Risk factors for unplanned transfer to intensive care within 24 hours of admission from the emergency department in an integrated healthcare system. J Hosp Med. 2013;8(1):13-9.
7. Arntz H, Willich S, Schreiber C, et al. Diurnal, weekly and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. Eur Heart J 2000;21(4):315-20.
8. Spielberg C, Falkenhahn D, Willich S, et al. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. Am Heart J 1996;132(2):579-85.
9. Reavey M, Saner H, Paccaud F, Marquez-Vidal P. Exploring the periodicity of cardiovascular events in Switzerland: Variation in deaths and hospitalizations across seasons, day of the week and hour of the day. Int J Cardiol 2013;168(3):2195-200.
10. Maldonado G, Kraus J. Variation in suicide by time of day, day of the week, month, and lunar phase. Suicide Life Threat Behav 1991;21(2):174-87.
11. Macfarlane A, White G. Deaths: the weekly cycle. Population Trends 1977;7:7-8.
12. Shigematsu K, Watanabe Y, Nakano H, et al. Weekly variations of stroke occurrence: an observational cohort study based on the Kyoto Stroke Registry, Japan. BMJ Open 2015;5:e006294.
13. Zhang H, Schaubel D, Kalbfleisch J, et al. Dialysis outcomes and analysis of practice patterns suggests dialysis schedule affects day-of-week mortality. Kidney Internat 2012;81:1108-15.
14. Trudeau R. Monthly and daily patterns of death. Health Reports 1997;9(1):43-50.
15. Berument H, Kiymaz H. The Day of the Week Effect on Stock Market Volatility J Econ Finance 2001; 25(2):181-91.
16. The weekend effect. http://calendar-effects.behaviouralfinance.net/weekend-effect/
17. Bryson A, Forth J Are There Day of the Week Productivity Effects? Centre for Economic Performance, London School of Economics and Political Science, July 2007 http://cep.lse.ac.uk/pubs/download/mhrldp0004.pdf
18. Akay A, Martinsson P. Sundays Are Blue: Aren't They? The Day-of-the-Week Effect on Subjective Well-Being and Socio-Economic Status. IZA DP No. 4563 November 2009, Institute for the Study of Labour in Bonn. https://ideas.repec.org/p/hhs/gunwpe/0397.html
19. Taylor M. Tell me why I don't like Mondays: Investigating day of the week effects on job satisfaction and psychological well-being. Institute for Social and Economic Research University of Essex ISER Working Papers Number 2002-22, October 2002. https://www.iser.essex.ac.uk/research/publications/working-papers/iser/2002-22.pdf
20. Ryan R, Bernstein J, Brown K. Weekends, Work, and Well-Being: Psychological Need Satisfactions and Day of the Week Effects on Mood, Vitality, and Physical Symptoms. Journal of Social and Clinical Psychology 2010;29(1):95-122.
21. Colder C, Lloyd-Richardson E, Flaherty B, et al. The natural history of college smoking: Trajectories of daily smoking during the freshman year. Addictive Behav 2006;31(12):2212-22.
22. Laird D. Relative performance of college students as conditioned by time of day and day-of-week. J Exper Psychol 1925;8(1):50-63.
23. Laux P, Kuntsmann H. Detection of regional weekly weather cycles across Europe. Environ Res Lett 2008;3:044005
24. Goldstein H. The biochemical variability of the individual in relation to personality and intelligence. J Exper Psyhcol 1935;18(3):348-71.

25. Ozdemir B, Sinha S, Karthikesalingham A, et al. Mortality of emergency general surgical patients and associations with hospital structures and processes. Brit J Anaesth 2016;116(1):54-62.
26. Aylin P, Alexandrescu R, Jen M, et al. Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. BMJ 2013;346:f2424.
27. Ruiz M, Bottle A, Aylin P. The global comparators project: international comparison of 30-day in-hospital mortality by day of the week. BMJ Qual Saf 2015; doi:10.1136/bmjqs-2014-003467
28. Palmer W, Bottle A, Aylin P. Association between day of delivery and obstetric outcomes: observational study. BMJ 2015;351:h5774
29. Freemantle N, Richardson M, Wood J, et al. Weekend hospitalization and additional risk of death: An analysis of inpatient data. J R Soc Med 2012;105:74-84.
30. Roberts S, Thorne K, Akbari A, et al. Mortality following stroke, the weekend effect and related factors: Record linkage study. PLoS ONE 2015;10(6):e0131836
31. James M, Wald R, Bell C, et al. Weekend hospital admission, acute kidney injury, and mortality. J Amer Soc Nephrol 2010;21:845-51.
32. Horwich T, Hernandez A, Liang L, et al. Weekend hospital admission and discharge for heart failure: association with quality of care and clinical outcomes. Am Heart J 2009;158(3)451-8.
33. Desai V, Gonda D, Ryan S, et al. The effect of weekend and after-hours surgery on morbidity and mortality rates in pediatric neurosurgery patients. J Neurosurg Pediatr 2015;25:1-6.
34. Vest-Hansen B, Riis A, Sorensen H, Christiansen C. Out-of-hours and weekend admissions to Danish medical departments: admission rates and 30-day mortality for 20 common medical conditions. BMJ Open 2015;5(3):e006731.
35. Coiera E, Wang Y, Magrabi F, et al. Predicting cumulative risk of death during hospitalization by modelling weekend, weekday and diurnal mortality risks. BMC Health Serv Res 2014;14:226.
36. Magid D, Wang Y, Herrin J, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute-ST-segment elevation myocardial infarction. JAMA 2005;294(22):2846-7.
37. Attenello F, Wen T, Cen S, et al. Incidence of “never events” among weekend admissions versus weekday admissions to US Hospitals: national analysis, BMJ 2015;350:h1460.
38. Hong J, Kang H, Lee S. Comparison of case fatality rates for acute myocardial infarction in weekday vs weekend admissions in South Korea. Circ J 2010;74(3):496-502.
39. Dorn S, Shah N, Berg B, Naessens J. Effect of weekend hospital admission on gastrointestinal hemorrhage outcomes. Dig Dis Sci 2010;55(6):1658-66.
40. Ananthakrishnan A, McGinley E, Saeian K. Outcomes of weekend admission for upper gastrointestinal hemorrhage: a nationwide analysis. Clin Gastroenterol Hepatol 2009;7(3):296-302.
41. Kostis W, Demissie K, Marcella S, et al. Weekend versus weekday admission and mortality from myocardial infarction. N Engl J Med 2007;356(11):1099-109.
42. Hasegawa Y, Yoneda Y, Okuda S, et al. The effect of weekends and holidays on stroke outcome in acute stroke units. Cerebrovasc Dis 2005;20(5):325-31.
43. Hansen K, Hvelplund A, Abidstrom S, et al. Prognosis and treatment in patients admitted with acute myocardial infarction on weekends and weekdays from 1997 to 2009. Int J Cardiol 2013;168(2):1167-73.
44. Brims F, Asiimwe A, Andrews N, et al. Weekend admission and mortality from acute exacerbations of chronic obstructive pulmonary disease. Clin Med 2011;11(4):334-9.
45. Carr B, Jenkins P{, Branas C, et al. Does the trauma system protect against the weekend effect? J Trauma 2010;69(5|):1042-7.
46. Inoue T, Fushimi K. Weekend versus weekday admission and in-hospital mortality from ischaemic stroke in Japan, J Stroke Cerebrovasc Dis 2015;pii:S1052-3057(15)00440-1.
47. Johnson D, Clayton P, Cho Y, et al. Weekend compared to weekday presentations of peritoneal dialysis-associated peritonitis. Perit Dial Int 2012;32(5):516-24.
48. McKinney J, Deng Y, Kasner S, Kostis J. Comprehensive stroke centers overcome the weekend versus weekday gap in stroke treatment and mortality, Stroke 2011;42(9):2403-9.

49. Lee K, Ng I, Ang B. Outcome of severe head injured patients admitted to intensive care during weekday shifts compared to nights and weekends. Ann Acad Med Singapore 2008;37(5):390-6.
50. Luyt C, Combes A, Aegerter P, et al. Mortality among patients admitted to intensive care units during weekday day shifts compared with "off" hours. Crit Care Med 2007;35(1):3-11.
51. Arabi Y, Alshimemeri A, Taher S. Weekend and weeknight admissions have the same outcome as weekday admissions to an intensive care unit with onsite intensive coverage. Crit Care Med 2006;34(3):605-11.
52. Worni M, Ostbye T, Gandhi M, et al. Laparoscopic appendectomy outcomes on the weekend and during the week are no different: a national study of 151,774 patients. J World Surg 2012;36(7):1527-33.
53. Goldacre M, Maisonneuve J. Mortality from meningococcal disease by day of the week: English national linked database study. J Public Health (Oxf.) 2013;35(3):413-21.
54. Wilson E, Yang W, Schrauben S, et al. Sundays and mortality in patients with AKI. Clin J Am Soc Nephrol 2013;8(11):1863-9.
55. Boylan M, Rosenbaum J, Adler A, et al. Hip fracture and the weekend effect: Does weekend admission affect patient outcomes? Am J Orthop (Belle Mead NJ) 2015;44(10):458-64.
56. Roberts S, Thorne K, Akbari A, et al. Mortality following stroke, the weekend effect and related factors: Record linkage study. PLoS One 2015;10(6):e0131836.
57. Zapf M, Kothari A, Markossian T, et al. The "weekend effect" in urgent general operative procedures. Surgery 2015;158(2):508-14.
58. Goldstein S, Papandira D, Aboagye J, et al. The "weekend effect" in pediatric surgery – increased mortality for children undergoing urgent surgery during the weekend. J Paediatr Surg 2014;49(7):1087-91.
59. Orandi B, Selvarajah SD, Orion K, et al. Outcomes of nonelective admissions for lower extremity ischemia. J Vasc Surg 2014;60(6):1572-9.
60. Goodman E, Reilly A, Fisher B, et al. Association of weekend admission with hospital length of stay, time to chemotherapy, and risk of respiratory failure in pediatric patients with newly diagnosed leukemia at freestanding US children's hospitals. JAMA Pediatr 2014;168(10):925-31.
61. Schmid M, Ghani K, Choueiri T, et al. An evaluation of the 'weekend effect' in patients admitted with metastatic prostate cancer. BJU Int 2015;116(6):9811-9.
62. Isogai T, Yasunaga H, Matsui H, et al. Effect of weekend admission for acute myocardial infarction on in-hospital mortality: a retrospective cohort study. Int J Cardiol 2015;179:315-20.
63. Kim H, Kim K, Cho Y, et al. The effect of admission at weekends on clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome and its contributory factors. J Korean Med Sci 2015;30(4):414-25.
64. Mikulich O, Callaly E, Bennett K, et al. The increased mortality associated with a weekend emergency admission is due to increase illness severity and altered case-mix. Acute Med 2011;10(4):182-7.
65. Kazley A, Hillman D, Johnston K, Simpson K. Hospital care for patients experiencing weekend vs weekday stroke: a comparison of quality and aggressiveness of care. Arch Neurol 2010;67(1):39-44.
66. Jiang F, Zhang J, Qin X. "Weekend effects" in patients with intracerebral hemorrhage. Acta Suppl 2011;111:1589-96.
67. Fedorets V, Dul'skii V, Mozerova E, et al. All-cause mortality among men of elderly and senile age depending on day of week, on season and changing to daylight saving time for a 13-year period, Adv Gerontol 2012;25(2):233-7. [*Translation from Russian*]
68. Hoh B, Chi Y, Waters M, et al. Effect of weekend compared to weekday stroke admission on thrombolytic use, in-hospital mortality, discharge disposition, hospital charges, and length of stay in the Nationwide Inpatient Sample Database, 2002 to 2007. Stroke 2010;41(10):2323-8.
69. Tufegdzic M, Panic N, Boccia S, et al. The weekend effect in patients hospitalized for upper gastrointestinal bleeding: a single-center 10-year experience. Eur J Gastroenterol Hepatol 2014;26(7):715-20.
70. 20Jairath V, Kahan B, Logan R, et al. Mortality from acute upper gastrointestinal bleeding in the United Kingdom: does it display a "weekend effect"? Am J Gastroenterol 2011; 10-6(9): 162-8.

71. Shaheen A, Kaplan G, Myers R. Weekend versus weekday admission and mortality from gastrointestinal hemorrhage caused by peptic ulcer. Clin Gastroenterol Hepatol 2009;7(3):303-10.
72. Ricciardi R, Nelson J, Francone T, et al. Do patient safety indicators explain increased weekend mortality? J Surg Res 2015; piiS0022-4804(15)00804-5.
73. Cram P, Hillis S, Barnett M, Rosenthal G. Effects of weekend admission and hospital teaching status on in-hospital mortality. Am J Med 2004;117:151-7.
74. Stone G, Aruasa W, Tarus T, et al. The relationship of weekend admission and mortality on the public medical wards at a Kenyan referral hospital. Int Health 2015;7(6):433-7.
75. Bell C, Redelmeier D. Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med 2001;345(9):663-8.
76. O'Brien E, Rose K, Shahar E, Rosamond W. Stroke mortality, clinical presentation and day of arrival: The atherosclerosis risk in communities (ARIC) study. Stroke Res Treatment 2011; ID 383012
77. Needleman J, Buerhaus P, Pankratz S, et al. Nurse staffing and inpatient hospital mortality. New Engl J Med 2011;364:1037-45.
78. McHugh M, Kelly L, Smith H, et al. Lower mortality in magnet hospitals. Med Care 2013;51(5): 382-388.
79. Aiken L, Sloane D, Bruyneel L, et al. Nurse staffing and education and hospital mortality in nine European countries: a retrospective observational study. Lancet,14;383:1824-30.
80. Turin T, Kita Y, Rumana N, et al. Case fatality and day-of-week: Is the weekend effect an artefact? Cerebrovasc Dis 2008;26:696-711.
81. Barnett M, Kaboli P, Sirio C, Rosenthal G. Day of the week of intensive care admission and patient outcomes: A multisite regional evaluation. Medical Care 2002;40(6):530-9.
82. Yergens D, Ghali W, Faris P, et al. Assessing the association between occupancy and outcome in critically ill hospitalized patients with sepsis. BMC Emerg Med 2015; 15:31.
83. Jones R. Volatility in bed occupancy for emergency admissions. Brit J Healthc Manage 2011;17(9):424-430.
84. Jones R. Optimum bed occupancy in psychiatric hospitals. Psychiatry On-Line 2013; http://www.priory.com/psychiatry/psychiatric_beds.htm
85. Jones R. Hospital bed occupancy demystified and why hospitals of different size and complexity must operate at different average occupancy. Brit J Healthc Manage 2011;17(6):242-8.
86. Campbell M, Jacques R, Fotheringham J, et al. Developing a summary hospital mortality index: retrospective analysis in English hospitals over five years. BMJ 2012;344:e1001.
87. Bo M, Massaia M, Raspo S, et al. Predictive factors of in-hospital mortality in older patients admitted to a medical intensive care unit. J Am Geriat Soc 2003;51(4): 529-33.
88. Kellett J, Deane B. The simple clinical score predicts mortality for 30 days after admission to an acute medical unit. Q J Med 2006;99:771-81.
89. Horne B, May H, Muhlestein J, Ronnow B, Lappe D, Renlund G, et al (2009) Exceptional mortality prediction by risk scores from common laboratory tests. Amer J Med 122: 550-558.
90. Gagne J, Glynn R, Avorn J, et al. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749-59.
91. Hunziker S, Stevens J, Howell M. Red cell distribution width and mortality in newly hospitalized patients. Amer J Med 2012;125(3): 283-91.
92. Mohammed M, Rudge G, Wood G, et al. Which is more useful in predicting hospital mortality – dichotomised blood test results or actual test values? A retrospective study in two hospitals. PLOS ONE 2012;7(10)e46860
93. Mitnitski A, Collerton J, Martin-Ruiz C, et al. Age-related frailty and its association with biological markers of ageing. BMC Med 2015;13:161
94. Xu M, Tam B, Thabane L, Fox-Robichaud A. A protocol for developing early warning score models from vital signs data in hospitals using ensembles of decision trees. BMJ Open 2015;5:e008699
95. O'Sullivan E, Callely E, O'Riordan D, Silke B. Predicting outcomes in emergency medical admissions – role of laboratory data and co-morbidity. Acute Med 2012;11(2):59-65.

96. Mathers C. Births and perinatal deaths in Australia: variations by day-of-week. J Epidemiol Community Health 1983; 37(1): 57-62.
97. Pendlebury S, Lovett N, Smith S, et al. Observational longitudinal study of delirium in consecutive unselected medical admissions: age-specific rates and associated factors, mortality and re-admission. BMJ Open 2015;5: e007808.
98. Louis D, Robeson M, McAna J, et al. Predicting risk of hospitalization or death: a retrospective population-based analysis. BMJ Open 2014;4:e005223
99. Melzer D, Tavakoly B, Winder R, et al. Much more medicine for the oldest old: trends in UK electronic clinical records. Age and Ageing 2015;44:46-53.
100. Papachristofi O, Sharples L, Mackay J, et al. The contribution of the anaesthetist to risk-adjusted mortality after cardiac surgery. Anaesthesia 2016;71(2):138-146.
101. Baines R, Langelaan M, de Bruijne M, Wagner C. Is researching adverse events in hospital deaths a good way to describe patient safety in hospitals: a retrospective patient record review study. BMJ Open 2015;5:e007380.
102. Laupland K, Shahpori R, Kirkpatrick A, Stelfox H. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. J Crit Care 2008;23(3): 317-24.
103. Health and Social Care Information Centre (2016) Seven-day Services - England, Provisional, July 2014 - June 2015, Experimental statistics. http://www.hscic.gov.uk/catalogue/PUB19882
104. Jones R. Maternity bed occupancy: all part of the equation. Midwives Magazine 2012; 15(1): Available: http://www.rcm.org.uk/midwives/features/all-part-of-the-equation/
105. Jones R. A simple guide to a complex problem – maternity bed occupancy. Brit J Midwifery 2012;20(5): 351-357.
106. Jones R. A guide to maternity costs – why smaller units have higher costs. Brit J Midwifery 2013;21(1):54-59.
107. Meacock R, Doran T, Sutton M. What are the costs and benefits of providing comprehensive seven-day services for emergency hospital admissions? Health Econ 2015;24(8):907-12.
108. Vickers A, Van Calster B, Steyerberg E. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ 2016;352:i6
109. Kuntz L, Mennicken R, Scholtes S. Stress on the ward: evidence of safety tipping points in hospitals. Manage Sci. 2014;61:754-71.
110. Concha O, Tallego B, Delaney G, Coiera E. Do variations in hospital mortality patterns after weekend admission reflect reduced quality of care or different patient cohorts? A population-based study. BMJ Qual Saf 2014;23(3):215-22.
111. Jones R. A presumed infectious event in England and Wales during 2014 and 2015 leading to higher deaths in those with neurological and other disorders. J Neuroinfectious Dis 2016;7(1):1000213 doi: 10.4172/2314-7326.1000213
112. Jones R. Deaths in English Lower Super Output Areas (LSOA) show patterns of very large shifts indicative of a novel recurring infectious event. SMU Medical Journal 2016;3(2):23-36.
113. Jones R. Rising emergency admissions in the UK and the elephant in the room. Epidemiology (Sunnyvale): Open Access 2016;6(4):1000261. doi: 10.4172/2161-1165.1000261
114. Jones R. A 'fatal' flaw in hospital mortality models: How spatiotemporal variation in all-cause mortality invalidates hidden assumptions in the models. FGNAMB 2015;1(3):82-96. doi: 10.15761/FGNAMB.1000116
115. Jones R. Links between bed occupancy, deaths and costs. Brit J Healthc Manage 2015;21(11):544-5.
116. Jones R. Hospital bed occupancy and deaths (all-cause mortality) in 2015. Brit J Healthc Manage 2016;22(5): 283-5.
117. Jones R. Clear the decks of Summary Hospital-level Mortality Indicator. Brit J Healthc Manage 2016;22(6):335-8.
118. Jones R. Bed occupancy and hospital mortality. Brit J Healthc Manage 2016;22(7):380-1.
119. Jones R. Hospital deaths and length of stay. Brit J Healthc Manage 2016;22(8):424-5.

120. Jones R. Trends in crude deaths rates in English hospitals. Brit J Healthc Manage 2016;22: *in press*.
121. Jones R. Hospital mortality rates and changes in activity. Brit J Healthc Manage 2016;22: *in press*.

APPENDIX

Table A1: Example of interpolation history for one patient (interpolated values are in bold italic)

		Raw Test Results												
Date	Day	HB	HCT	MCH	MCHC	RBC	RDW	PLT	ALB	GLOB	ALB:GLOB	CRP	ALP	AST
12/01/12	5	102	0.3	28	343	3.64	20.8	101	38	15	2.53	10.4	97	22
18/01/12	4	101	0.29	28.1	345	3.59	20.5	157	40	18	2.22	18.4	97	22
30/01/12	2	98	0.29	29	343	3.38	19.8	82	35	19	1.84	33	97	22
08/02/12	4	96	0.27	29.1	354	3.3	18.8	211	37	19	1.95	5.5	124	13
09/02/12	5	98	0.27	29.5	359	3.32	19	213	38	18	2.11	3.7	106	19
16/02/12	5	85	0.24	29.8	350	2.85	18	107	35	17	2.06	7.1	90	21
29/02/12	4	88	0.25	29.7	346	2.96	17.9	159	37	21	1.76	7.5	80	22
09/03/12	6	77	0.21	30.1	360	2.56	16.2	64	35	17	2.06	74	199	28
10/03/12	7	71	0.2	30.5	359	2.33	16	39	32	15	2.13	96	64	36
12/03/12	2	107	0.31	29.7	345	3.6	16.3	43	33	21	1.57	108	***90***	***34***
13/03/12	3	111	0.32	29.6	351	3.75	16.3	60	34	22	1.55	60	126	31
15/03/12	5	113	0.32	29.7	358	3.8	15.9	102	36	22	1.64	***52***	***116***	***29***
21/03/12	4	111	0.32	29.4	352	3.77	15.3	191	38	22	1.73	***48***	***106***	***27***
02/04/12	2	92	0.26	29.8	352	3.09	16.7	94	34	20	1.70	***40***	***99***	***25***
12/04/12	5	91	0.26	29.6	357	3.07	17.4	133	38	18	2.11	38	92	23
03/05/12	5	104	0.3	31	342	3.36	17.5	168	38	19	2.00	***41***	***73***	***22***
17/05/12	5	102	0.3	29.7	346	3.44	15	115	37	19	1.95	45	54	21
26/06/12	3	115	0.33	29.1	352	3.95	13.7	141	38	18	2.11	1.8	61	28
03/07/12	3	112	0.32	29.1	350	3.85	14	91	37	19	1.95	1.8	85	18
30/07/12	2	122	0.35	28.2	354	4.32	13.8	132	41	17	2.41	233	88	34
30/08/12	5	118	0.34	28	350	4.21	14.1	126	39	19	2.05	***175***	***98***	***29***
03/09/12	2	118	0.34	28	349	4.22	14.1	120	39	20	1.95	***117***	***108***	***24***
15/09/12	7	117	0.33	28	358	4.18	15.1	66	36	26	1.38	***59***	***118***	***19***
16/09/12	1	101	0.29	27.7	349	3.65	14.9	85	31	19	1.63	1.8	127	13
17/09/12	2	***107***	***0.32***	***27.6***	***347***	***3.88***	***15***	***115***	30	20	1.50	***6***	***101***	***14***
17/09/12	2	113	0.33	27.4	345	4.12	15.1	146	32	21	1.52	10.3	***75***	***15***
18/09/12	3	94	0.27	27.2	343	3.46	15.1	143	28	22	1.27	1.8	54	15
19/09/12	4	91	0.26	27.7	349	3.28	15.5	203	25	26	0.96	1.8	48	21
19/09/12	4	96	0.28	27.4	349	3.5	15.4	267	26	22	1.18	***30***	***61***	***26***
20/09/12	5	102	0.29	27.6	347	3.69	15.9	430	27	23	1.17	58	74	29
21/09/12	6	92	0.26	28	350	3.29	16	298	26	29	0.90	54	125	20
22/09/12	7	92	0.27	27.7	339	3.32	16.3	292	28	23	1.22	31	176	29
23/09/12	1	90	0.28	27.4	327	3.29	16.4	231	28	21	1.33	2.8	50	17
24/09/12	2	96	0.3	27.5	324	3.49	16.7	240	29	20	1.45	4.9	66	26
25/09/12	3	89	0.28	27.6	321	3.22	17.6	171	28	19	1.47	1.8	48	17
26/09/12	4	102	0.31	28.4	325	3.59	19.1	159	29	21	1.38	1.8	54	21
27/09/12	5	104	0.34	27.6	308	3.77	19.6	***127***	30	***20***	1.50	1.8	54	15
28/09/12	6	94	0.3	28.1	314	3.34	19.6	96	28	19	1.47	27	75	13
29/09/12	7	99	0.317	27.9	312	3.55	19.5	99	28	19	1.47	101	82	12
30/09/12	1	93	0.287	28.7	324	3.24	19.3	84	26	18	1.44	56	***134***	***13***
01/10/12	2	88	0.266	28.5	331	3.09	19.1	61	27	17	1.59	96	185	13
02/10/12	3	82	0.248	28.3	331	2.9	18.7	48	27	17	1.59	***118***	***150***	***65***
03/10/12	4	75	0.23	27.9	326	2.69	18.5	32	25	16	1.56	141	115	116
04/10/12	5	96	0.285	28.3	337	3.39	17.9	38	25	16	1.56	1.8	52	27
04/10/12	5	83	0.257	27.7	323	3	18.2	33	22	18	1.22	95	53	149
05/10/12	6	82	0.255	27.7	322	2.96	18.2	36	22	17	1.29	15.8	150	62

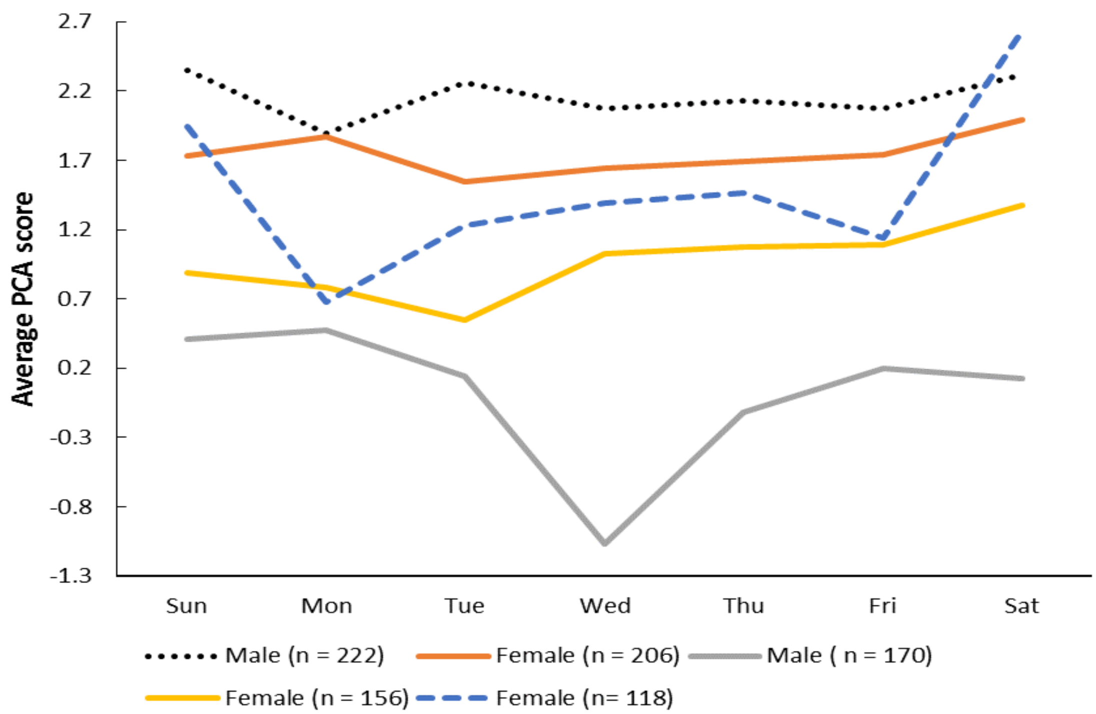

Fig. A1. Day-of-week profile calculated for 5 patients

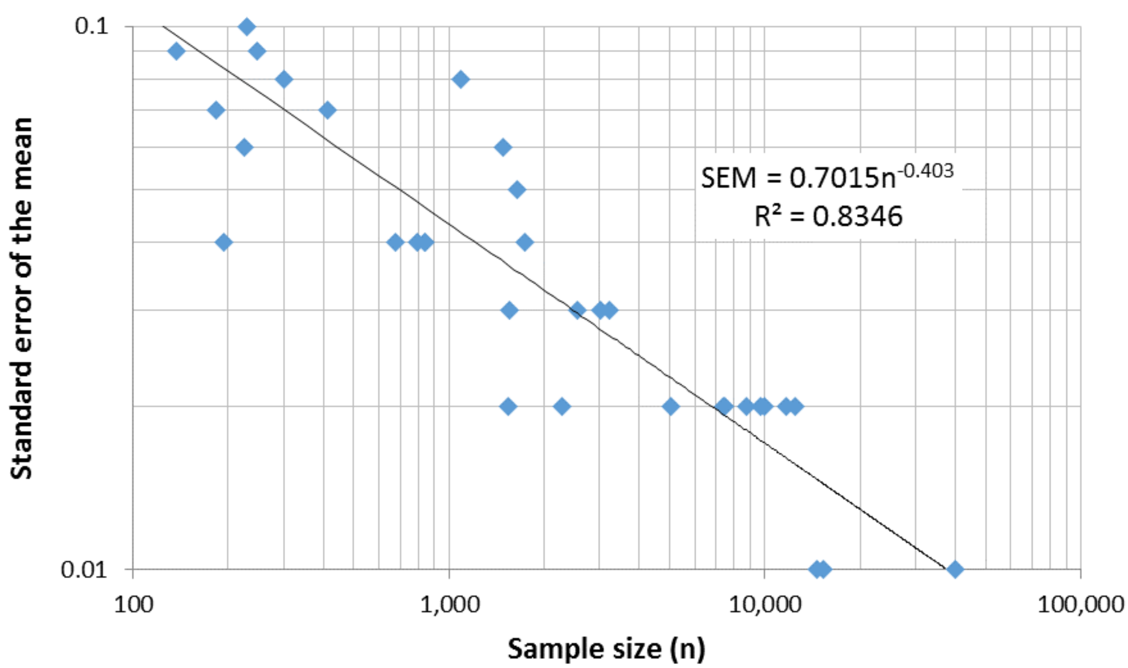

Fig. A2. Relationship between sample size and standard error of the mean

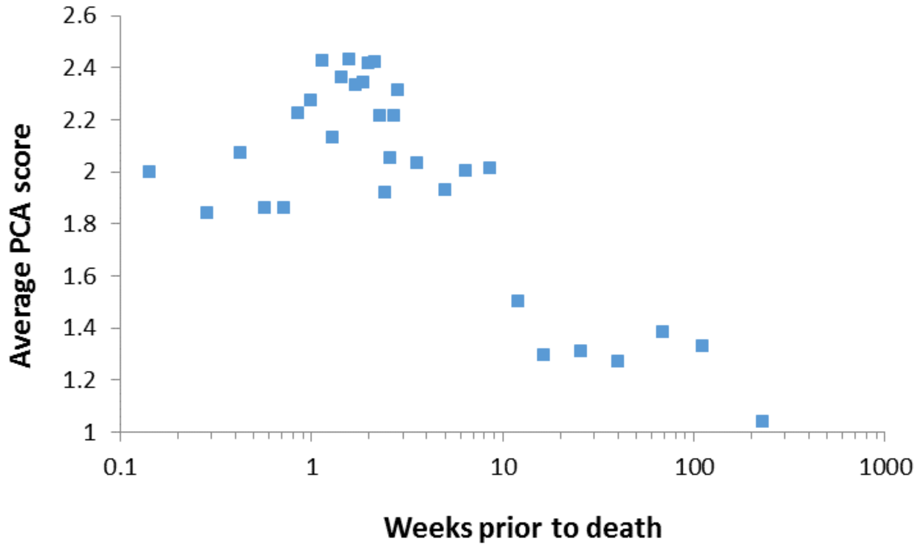

Fig. A3. Average PCA score in the weeks prior to death for the cohort of patients who spend time in the intensive care unit

There are 7,888 PCA measurements from 368 patients prior to in-hospital death. The x-axis is a log scale to enable better discrimination of the differences in average PCA score close to death. Highest number of PCA values (n=372) is on the day prior to death. Beyond 13 days prior to death there are less than 100 measurements per day, and less than 10 per day beyond 100 days prior to death. The final data point is the average of everything beyond three years prior to death.

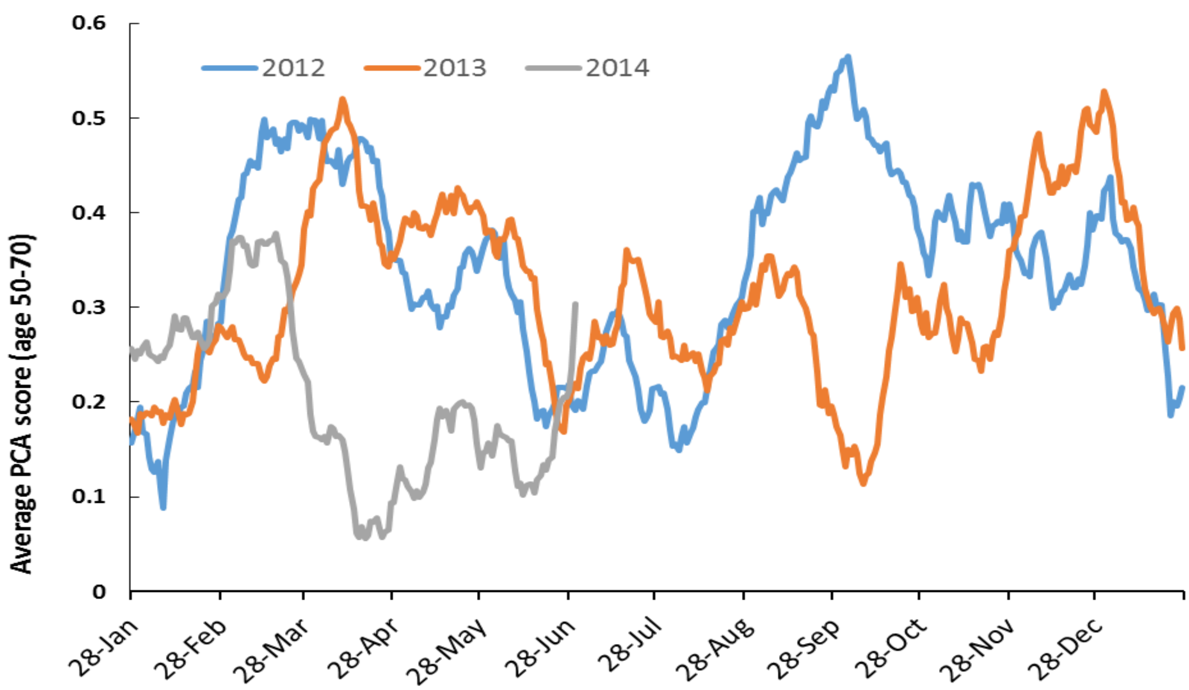

Fig. A4. Running 28 day average PCA score for inpatients aged 50-70 (n>1,300 for 28-day average)

A running 28-day average acts as a frequency filter to detect events which affect population health with a 28-day duration. Other frequency filters can be applied to detect events lasting 7 and 365 days (data not shown). For an *explanation of the use of running averages and running totals see references [111-114]. The key point is the utility of the PCA score to translate blood biochemistry into a potentially useful tool for population health screening.*

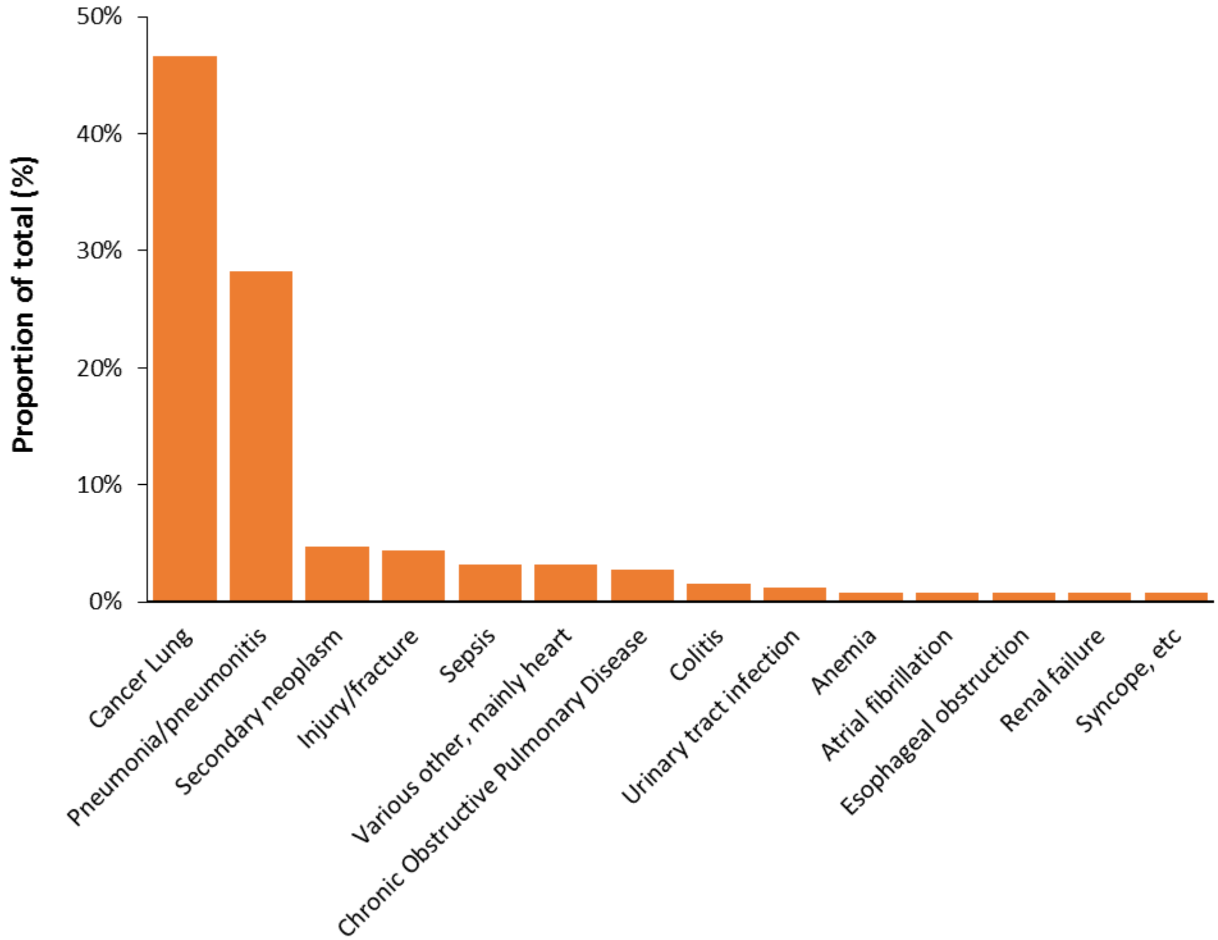

Fig. A5. Reason for final admission (morbidity coding) involving in-hospital death or death within 30 days of discharge for persons having a cause of death (mortality coding) listed as neoplasm of lung (n = 251 persons)