

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Out of Hours and Weekend Admissions to Danish Medical Departments: Admission Rates and 30-Day Mortality for 20 Common Medical Conditions
AUTHORS	Vest-Hansen, Betina; Riis, Anders Hammerich; Sørensen, Henrik T.; Christiansen, Christian

VERSION 1 - REVIEW

REVIEWER	Deepak Bhonagiri UNSW Sydney Australia
REVIEW RETURNED	12-Oct-2014

GENERAL COMMENTS	<p>This is an important area of study and an interesting report. There are a few issues I would like to be addressed</p> <ol style="list-style-type: none">1- please state in the manuscript that the research design is a retrospective database audit2- the description of the database seems OK but it will be helpful to the reader to know where it is located and how it was accessed.3- there are no details regarding human research ethics approval or lack of requirement of the same. In many jurisdictions this study would need approval from an ethics board, generally and low and negligible risk research approval4- it will be interesting to see a table with the top 5-6 causes of mortality compared in the 4 groups and adjusted for age and sex5- you mention standardised mortality for age and sex on page 15. Does this mean mortality adjusted for age and sex based on a formula from the book referenced? my understanding of "standardised mortality" is that the observed mortality is divided by the expected mortality based on a severity scoring system6- I think you will benefit from some further statistics and statistical advice especially in terms of performing multivariate analysis and representing the differences in mortality based on the CCI scores. What a reader wants to know is if the increased mortality observed in some groups can all be explained by increased CCI scores. I note you mention that there was no significant difference in CCI scores in the 4 groups but we want to know that in the patients who die7- ICU admission is a useful surrogate of severity of illness if admission and discharge criteria to ICU are standardised or if some ICU severity score like APACHE II/III/IV or SAPS or SOFA is available on the database. The reader will want to know that ICU admission at nights were truly indicated
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REVIEWER	Chris Isles Education Centre Dumfries Infirmary Dumfries DG1 4AP
REVIEW RETURNED	16-Oct-2014

GENERAL COMMENTS	<p>I enjoyed reading this paper which addresses an important topic and adds to what is already known, but I think it could be better:</p> <ol style="list-style-type: none"> 1) I struggled with the times of admission in the methods section. I assume 'Monday night from 0.00pm to 759am' must mean Sunday night from midnight to 759am on Monday morning. 2) Authors might consider describing 'off hours' as 'out of hours' 3) Could Table 1 show p values to indicate whether the distribution of age, gender, CCI, marital status etc was the same or different across the 4 admission categories. 4) Instead of choosing 20 common medical conditions it might have been more interesting to have looked at the 20 medical admissions with the highest mortality. This would eliminate those conditions with very low 30 day mortality such as suspected MI, syncope, TIA, hypertension as these disorders don't really add anything to the debate 5) I would like, for obvious reasons (Smith et al EMJ 2014), the authors to acknowledge that the weekend effect might in fact be driven by higher mortality among patients admitted on public holidays when the whole hospital shuts down for 3 or 4 days. 6) My last comment is perhaps the one I feel is most important. The authors findings when published will be seized upon by commentators and the media as further evidence that hospitals are unsafe at weekends. There will then be demands that hospitals are staffed at weekends as they are during the week. This must sound incredibly sensible to a lay person but I am not sure the evidence presented necessarily supports such a course of action. I can illustrate what I mean by drawing attention to the hourly admission for bacteraemia/septicaemia which shows a four fold variation between the different times of admission. It is difficult to believe that bacteraemia/septicaemia occurs 4 times more commonly between the hours of 8 and 5pm on a weekday than it does between 10pm and 9am on a weekend. It follows that more patients with mild bacteraemia/septicaemia are admitted on weekdays and only severe bacteraemia/septicaemia are admitted overnight at weekends. If that is the case then it would come as no surprise to find that mortality for bacteraemia/septicaemia admitted overnight at weekends is higher, when expressed as a percentage of patients admitted. I don't believe that this negates the authors findings but I do feel it deserves a bit more discussion.
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REVIEWER	Bo E Madsen Mayo Clinic, Rochester, MN USA
REVIEW RETURNED	03-Nov-2014

GENERAL COMMENTS	<p>I would rather see the admission rate per hour per 100.000 than the apparent per hour per population. This would allow other countries to compare their admission rates for similar conditions in an easier manner. Similarly, the information regarding the mortality rates should be specified.</p> <p>A table describing the number of deaths for each of the conditions based on the time of admission is needed in order to allow of calculation of the mortality rates.</p> <p>You write that the admission rates varied considerably between medical conditions. I think that it is the proportion of the admissions that you describe and not admission rates for the conditions. The proportion of admissions should be expected to vary as the prevalence and natural course varies considerably as well, e.g. some conditions have an acute onset, other have a slower onset.</p> <p>You write in your abstract conclusion that “weekend admissions were associated with the highest mortality for the majority of the conditions examined”, yet this appears to hold true for the aggregate measure but no statistically significant difference in the mortality rates for any of the 20 conditions is apparent except for stroke when analyzed by single condition. I think that it should be pointed out. You could supply the p values compared to your reference (Day time admissions) for the individual conditions and the aggregate.</p> <p>I would consider using the term “Emergency Department” rather than “Emergency room”</p> <p>You write that “Furthermore, admission rates for common medical conditions in these time periods may serve as a proxy of the changes in referral threshold and together with mortality rates add to the understanding of the weekend effect.” Based on the rates of ICU admissions for the various conditions it appears that the population that is admitted during non-office hours is sicker than the patients admitted during office hours. The same difference appears to be supported by your length of hospital stay data. It would be nice to see whether there is a statistically significant difference. I would also elaborate more on that in your discussion as this possibly explains the higher mortality that you see for off-hour admissions.</p> <p>You state that “In a subgroup analysis, the admission rate, 30-day mortality rate, and ICU admissions during the four time periods were analyzed only among patients admitted through the emergency room.” Does table S3 refer to this subgroup analysis? If it does it should be clearly stated in the table.</p> <p>It would be helpful if you elaborated on the structure of the Danish Health Care system. I think that the reader will want to know that GPs during day time hours often admit to departments and that during night time there is either the EDs or the vagtlaege who will</p>
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	<p>refer to the ED if (s)he think that the patient needs admission.</p> <p>Consider revising this part for better clarity “weekday off hours (Monday to Friday from 5.00 pm to 7.59 am, except Friday evening from 10.00 pm-11.59 pm and Monday night from 0.00 pm to 7.59 am), 15.4% as weekend daytime hours (Saturday and Sunday from”.</p> <p>“Urinary tract infection was the only condition associated with the highest mortality for admissions during weekday office hours (5.5% (95% CI 4.5-6.5%)).” Please supply the mortality rates for the non-weekday office hours in the text for immediate comparison and include the p values for the difference. Please supply the p value for the difference in mortality for stroke and anemia (page 15, line 43-52).</p> <p>It would be very interesting to compare the referral diagnosis to the discharge diagnosis but I realize that this is outside the scope of this paper.</p> <p>“We computed length of hospital stay as time from the index date to final hospital discharge, including in-hospital and inter-hospital transfers, except those occurring more than one day after a preceding discharge as they were considered readmissions rather than transfers”. I would delete “except those occurring more than one day after a preceding discharge as they were considered readmissions rather than transfers” as it should be clear that a discharged patient that is admitted to another hospital with a time interval interspersed is a readmission.</p> <p>In your discussion (key findings) you refer to the highest mortality rates being for weekend admissions for the majority of the conditions examined, again, I don’t think that there is a statistically significant difference. Same section you describe that “the proportion of patients arriving through the emergency room changed dramatically from weekday office hours to weekday off hours”. This is a function of the organization of the health care system and is very unlikely to be a patient population characteristic.</p> <p>Interpretation:</p> <ul style="list-style-type: none"> • “the overall reasons for admissions changed from office hours to off hours and weekend hours.” I am not convinced about this. The admissions rates changed but did the reasons, i.e. chief complaint or admissions diagnosis change? Fewer patients were admitted during off hours • “in conclusion, timing of first time admissions varied and weekend admissions were associated with the highest mortality for the majority of the conditions examined”. Yes, but not statistically significant unless as an aggregate. As I read the paper, I think that the conclusion is that fewer patients are admitted during off-hours and that they, based on their higher ICU admission rates, longer lengths of stays are sicker than the patients being admitted during the office hours.
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VERSION 1 – AUTHOR RESPONSE

Reviewer Name Deepak Bhonagiri

Institution and Country UNSW Sydney Australia

Please state any competing interests or state ‘None declared’: None

This is an important area of study and an interesting report. There are a few issues I would like to be addressed

1.1 Please state in the manuscript that the research design is a retrospective database audit

Reply: Our study is based on historic data from the Danish National Registry of Patients (DNRP). The data in this registry are entered prospectively independent of the current study. We would therefore prefer to call the study a historic cohort study using prospectively collected data. We believe it is important to keep "cohort study" as recommended in the STROBE guidelines for reporting observational studies.[1] (Page 6, Line 9)

1.2 The description of the database seems OK but it will be helpful to the reader to know where it is located and how it was accessed.

Reply: We have addressed the request from the reviewer and revised the section which describes the database to read as follows:

"The DNRP is a central medical registry covering both public and private hospitals that record information on all hospital admissions to non-psychiatric hospitals since 1977 and all visits to emergency departments and hospital specialist clinics since 1995. The record of each admission or visit is linked to the unique CPR number. In the study period, the DNRP was managed by the National Board of Health, but is currently managed by Statens Serum Institut (SSI). After necessary approvals, data from the DNRP can be accessed by researchers in Denmark by application to SSI." (Page 6, Lines 12-18)

1.3 There are no details regarding human research ethics approval or lack of requirement of the same. In many jurisdictions this study would need approval from an ethics board, generally and low and negligible risk research approval.

Reply: We have revised the manuscript to clearly state that ethical approval is not required for observational studies based on data from the DNRP.

The following sentence was added:

"Because these studies were based solely on data from administrative and medical databases, no further approval from the Ethics Committee was required." (Page 10, Lines 20-22)

1.4 It will be interesting to see a table with the top 5-6 causes of mortality compared in the 4 groups and adjusted for age and sex.

Reply: We agree with the reviewer that valid data on distribution of cause of death would be of interest. We have not included data from the Danish Cause of Death Registry in our data set for this study and were not able to obtain these data within the time frame of this response. In addition, the validity of causes of death is hampered by many deaths being recorded with non-specific causes.[2] We would therefore prefer not to include data on cause of death in the current study.

1.5 You mention standardized mortality for age and sex on page 15. Does this mean mortality adjusted for age and sex based on a formula from the book referenced? My understanding of "standardised mortality" is that the observed mortality is divided by the expected mortality based on a severity scoring system

Reply: We used direct standardization (applying observed age- and sex-specific rates to a standard population) and not indirect standardization (age- and sex-specific rates from a standard population applied to each study population to create Standardized Mortality Rates (SMR)) as described by the reviewer. To clarify the method used for standardization, we have changed the reference and added the sentence:

"To compute comparable 30-day mortality rates for different times of admission, we used direct standardization.[3] We applied the observed age- and sex-specific mortality rates to a standard population defined as the patients admitted during weekday office hours. That is, for each time period, we estimated what would have been the 30-day mortality rate in our standard population if the age-

and sex-specific mortality rates equaled those of the time period of interest.”
(Page 10, Lines 1-6)

1.6 I think you will benefit from some further statistics and statistical advice especially in terms of performing multivariate analysis and representing the differences in mortality based on the CCI score. What a reader wants to know is if the increased mortality observed in some groups can all be explained by increased CCI scores. I note you mention that there was no significant difference in CCI scores in the 4 groups but we want to know that in the patients who die.

Reply: The aim of our study was to describe differences in mortality rather than providing a fully-adjusted model, as we did not hypothesize that time of admission itself is associated with the outcome. However, to address the reviewer’s concern about the influence from the Charlson Comorbidity Index (CCI) score on mortality we have now included a sensitivity analysis including the CCI score in the standardization. Both the overall estimates (see Table R1 in the uploaded “Tables to decision letter”) and the estimates for the individual conditions were virtually unchanged. We have added the following sentence in the manuscript:

“In a sensitivity analysis, we included the CCI score in the standardization.”(Page 10, Lines 6-7)

“In the sensitivity analysis, which included age, sex, and the CCI score in the standardization of the 30-day mortality rates, similar results were found for the estimates in the overall cohort, as well as in the subgroups of common conditions.” (Page 19, Lines 1-3)

Table 1 in the manuscript displays a similar distribution of CCI levels in the four time periods. We also found similar CCI levels in patients who died (Table R2 in the uploaded “Tables to decision letter”). Thus, we do not believe that this provides any further information and we prefer not to include it in the manuscript.

1.7 ICU admission is a useful surrogate of severity of illness if admission and discharge criteria to ICU are standardised or if some ICU severity score like APACHE II/III/IV or SAPS or SOFA is available on the database. The reader will want to know that ICU admissions at nights were truly indicated.

Reply: In Denmark, SAPS II score has been implemented in the DNRP in 2009, but was still incomplete in our study period (2010) and was therefore not included in the study. Instead, we have computed the proportion receiving specific intensive care treatments, including mechanical ventilation, renal replacement therapy, and use of inotropes/vasopressors. These results are provided in Table 1b in the manuscript and the following paragraph was added to the Results section:

“In addition, we found that the proportion of patients receiving specific intensive care treatments, including mechanical ventilation, renal replacement therapy, and use of inotropes/vasopressors, was highest for the patients who were admitted during weekend nighttime hours. The proportion of the patients, who received multiple therapies were highest among the patients admitted outside office hours.”

(Page 14, Lines 8-13)

These ICU procedures can be considered as proxies for severity of illness, although some patients with severe illness will not be offered full therapy. There are no national or European guidelines for admission and discharge to an ICU. We acknowledge this limitation when using ICU admission as a proxy for severity of illness and have further emphasized this in the Discussion section.

(Page 23, Lines 6-11)

Reviewer Name Chris Isles

Institution and Country Education Centre

Dumfries Infirmary

Dumfries DG1 4AP

Please state any competing interests or state ‘None declared’: None declared

I enjoyed reading this paper which addresses an important topic and adds to what is already known, but I think it could be better:

2.1 I struggled with the times of admission in the methods section. I assume 'Monday night from 0.00pm to 759am' must mean Sunday night from midnight to 759 am on Monday morning.

Reply: We apologize and have corrected the error in the manuscript.

2.2 Authors might consider describing 'off hours' as 'out of hours'

Reply: As suggested by the reviewer, we have changed 'off hours' to 'out of hours'.

2.3 Could Table 1 show p values to indicate whether the distribution of age, gender, CCI, marital status etc was the same or different across the 4 admission categories.

Reply: The p value is not only a function of the strength of an association, but also of the sample size. According to the STROBE Statements, significance tests should be avoided in descriptive tables. We thus prefer not to include p-values in our descriptive table.1

2.4 Instead of choosing 20 common medical conditions it might have been more interesting to have looked at the 20 medical admissions with the highest mortality. This would eliminate those conditions with very low 30 day mortality such as suspected MI, syncope, TIA, hypertension as these disorders don't really add anything to the debate

Reply: In Table R3 from "Tables to decision letter", we have shown the top twelve reasons for admission among the patients who died within 30 days after admission. As shown in the table, we have included ten of the most frequent reasons for admission, which also were the most frequent reason for admission among the patients who died within 30 days after admission. We have not included neoplasm as an individual condition, as they were a rare reason for admission among medical patients who required an acute admission (1.3%). Similarly, the non-specific diagnosis Z039 was not included as an individual group, because we do not find that they add any clinically relevant knowledge. We believe that identifying important patient characteristics also for reasons with a low mortality adds to the understanding of the "weekend effect".

2.5 I would like, for obvious reasons (Smith et al EMJ 2014), the authors to acknowledge that the weekend effect might in fact be driven by higher mortality among patients admitted on public holidays when the whole hospital shuts down for 3 or 4 days.

Reply: In 2010, we identified the following public holidays, i.e. Easter (5 days), Whitsun (3 days), General Prayer Day (1 day + weekend), Ascension Day (2 days + weekend), Christmas (3 days), New Year's evening (2 days). In total, 4.2% of the study population was admitted during public holidays. The 30-day mortality for the medical patients who required acute admission during these public holidays was 5.8% (95% CI 5.2-6.3) compared to 5.3% (5.2-5.4) among the medical patients who required acute admission outside public holidays (both weekend and weekdays). We used direct standardization for the age and gender distribution of the study population admitted outside public holidays. Therefore, we are not convinced that the public holiday explains the observed increased mortality associated with an acute admission during weekend in Denmark, but we acknowledge that public holidays challenge acute hospital care similarly to weekends. The personal general practitioner is unavailable and the structure of acute hospital care is changed with less staff available for consultation. To acknowledge the contribution from the public holidays on the observed mortality, we have added the following in the Methods and Results sections:

"To acknowledge the effect from public holidays on our estimates, we analyzed the mortality associated with public holidays compared to all other days, including weekdays and weekend. We used direct standardization for the age and gender distribution of the study population admitted outside public holidays." (Page 10, Lines 14-18)

"The 30-day mortality for the medical patients who required acute admission during public holidays was 5.8% (95% CI 5.2-6.3) compared to 5.3% (95% CI 5.2-5.4) among the medical patients who required acute admission outside public holidays (weekend and weekdays).

(Page 19, Lines 7-10)

2.6 My last comment is perhaps the one I feel is most important. The authors findings when published will be seized upon by commentators and the media as further evidence that hospitals are unsafe at weekends. There will then be demands that hospitals are staffed at weekends as they are during the week. This must sound incredibly sensible to a lay person but I am not sure the evidence presented necessarily supports such a course of action. I can illustrate what I mean by drawing attention to the hourly admission for bacteraemia/septicaemia which shows a four fold variation between the different times of admission. It is difficult to believe that bacteraemia/septicaemia occurs 4 times more commonly between the hours of 8 and 5pm on a weekday than it does between 10pm and 9am on a weekend. It follows that more patients with mild bacteraemia/septicaemia are admitted on weekdays and only severe bacteraemia/septicaemia are admitted overnight at weekends. If that is the case then it would come as no surprise to find that mortality for bacteraemia/septicaemia admitted overnight at weekends is higher, when expressed as a percentage of patients admitted. I don't believe that this negates the authors finding but I do feel it deserves a bit more discussion.

Reply: We agree with the reviewer and have revised the "interpretation" section in the discussion to clarify our view. (Page 21, Lines 4-17)

And, we have revised the conclusion of the abstract to read as follows:

"While admission rates decreased from office hours to weekend hours there was an observed increase in mortality. This may reflect differences in severity of illness as the proportion admitted to an ICU increased during the weekend."

(Page 3, Lines 5-7)

Reviewer Name Bo E Madsen

Institution and Country Mayo Clinic, Rochester, MN

USA

Please state any competing interests or state 'None declared': None declared

3.1 I would rather see the admission rate per hour per 100,000 than the apparent per hour per population. This would allow other countries to compare their admission rates for similar conditions in an easier manner. Similarly, the information regarding the mortality rates should be specified.

Reply: We acknowledge the approach with the estimation of an admission rate per 100,000 to allow comparison. Therefore, we have provided the overall estimate of an hourly admission rate per 100,000 citizens (>=15 years) in the Results section.

We prefer to compute mortality rate per population per 30 days as we believe this provides the most clinically meaningful estimate.

3.2 A table describing the number of deaths for each of the conditions based on the time of admission is needed in order to allow of calculation of the mortality rates.

Reply: We have added the number of deaths for each of the conditions in Table 3.

3.3 You write that the admission rates varied considerably between medical conditions. I think that it is the proportion of the admissions that you describe and not admission rates for the conditions. The proportion of admissions should be expected to vary as the prevalence and natural course varies considerably as well, e.g. some conditions have an acute onset, other have a slower onset.

Reply: We prefer the term admission rates since we report the number of admission per hour, i.e., time (hour) is the denominator.

To discuss the natural variation in disease onset, we have added the following paragraph in the Discussion section:

"A few studies have examined the 24-h variation in admissions. Despite the different reasons for

admission, the overall admission pattern forms a curve with two peaks, one during the mid-morning hours and one during the late afternoon hours. [4-6] If this variation associates to a natural course of the diseases, a variation in prevalence and hence a variation in admission rates should be expected. However, this variation may more likely associate to the availability of the GPs.” (Page 22, Lines 7-12)

3.4 You write in your abstract conclusion that “weekend admissions were associated with the highest mortality for the majority of the conditions examined”, yet this appears to hold true for the aggregate measure but no statistically significant difference in the mortality rates for any of the 20 conditions is apparent except for stroke when analyzed by single condition. I think that it should be pointed out. You could supply the p values compared to your reference (Day time admissions) for the individual conditions and the aggregate.

Reply: For most conditions, 30-day mortality was slightly higher for patients admitted during weekends compared to patients admitted during weekday office hours. We acknowledge that our estimates of 30-day mortality in the subgroup of the common conditions were statistically imprecise with overlapping confidence intervals (CIs). We believe that this is due to lower number of patients in the subgroups, but this needs to be confirmed in future studies. Nevertheless, we find it acceptable and preferable to report the difference without statistical testing, as this would be more misleading. In “Recommendations for the conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” (http://www.icmje.org/recommendations/archives/2013_aug_urm.pdf) it is stated that one should “When possible, quantify findings and present them with appropriate indicators of measurement error and uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates.”

3.5 I would consider using the term “Emergency Department” rather than “Emergency room”

Reply: We have changed the term and supplied with a reference describing the emergency departments in Denmark to clarify the differences compared to US Emergency Departments.[7] In the Methods section, we have changed the description of the emergency departments to the following: “Acute hospital admission is also available through a 1-1-2 emergency call, which provides ambulance service to the patient. Finally, patients can present themselves to an emergency department on a 24-hour basis.⁷ However, in the study period some emergency departments implemented a mandatory preadmission assessment based on a telephone call before arrival.” (Page 7, Lines 2-6)

3.6 You write that “Furthermore, admission rates for common medical conditions in these time periods may serve as a proxy of the changes in referral threshold and together with mortality rates add to the understanding of the weekend effect.” Based on the rates of ICU admissions for the various conditions it appears that the population that is admitted during non-office hours is sicker than the patients admitted during office hours. The same difference appears to be supported by your length of hospital stay data. It would be nice to see whether there is a statistically significant difference. I would also elaborate more on that in your discussion as this possibly explains the higher mortality that you see for off-hour admissions.

Reply: We have elaborated on the length of stay data in a linear regression model adjusted for age and gender. The results are provided in Table R4 in “Tables to decision letter”.

After adjustment, the length of stay was found to be very similar for the patients admitted during weekday office hours and during weekend daytime hours. Weekday out of hours and weekend nighttime hours were associated with a slightly shorter length of stay. The same conclusion was found from the median length of stay. Therefore, we have not added these results in the manuscript.

3.7 You state that “In a subgroup analysis, the admission rate, 30-day mortality rate, and ICU admissions during the four time periods were analyzed only among patients admitted through the

emergency room.” Does table S3 refer to this subgroup analysis? If it does it should be clearly stated in the table.

Reply: Table S3 is the table which describes the proportion of patients admitted to an ICU in the subgroup of each of the common conditions. In the Results section, we have clarified that only Table S4 refers to this subgroup analysis of the patients admitted through the emergency department. (Page 19, Line 3-7)

3.8 It would be helpful if you elaborated on the structure of the Danish Health Care system. I think that the reader will want to know that GPs during day time hours often admit to departments and that during night time there is either the EDs or the vagtlaege who will refer to the ED if (s)he think that the patient needs admission.

Reply: In the Methods section, we have included the following description:

“General practitioners (GPs) have a key role in referring patients to the hospital departments since virtually all Danish residents are affiliated with a personal GP. Outside regular office hours, GPs serve the patients from central regional clinics providing both phone service and consultation.”(Page 6, Lines 21-22, Page 7, Lines 1-2)

3.9 Consider revising this part for better clarity “weekday off hours (Monday to Friday from 5.00 pm to 7.59 am, except Friday evening from 10.00 pm-11.59 pm and Monday night from 0.00 pm to 7.59 am), 15.4% as weekend daytime hours (Saturday and Sunday from”.

Reply: We have revised the section to read as follows:

“Time of admission was defined as weekday office hours, weekday out of hours, weekend daytime hours, and weekend nighttime hours. Public holidays, e.g., Easter and Christmas, were considered weekend days. Weekday office hours were from Monday to Friday from 8:00 am to 4:59 pm. Weekday off-hours were from Monday to Friday from 5:00 pm to 7:59 am, except Friday night from 10:00 pm-11:59 pm and Monday morning from 12:00 am to 7:59 am, which were considered part of the weekend. Weekend daytime hours were Saturday and Sunday from 9:00 am to 9:59 pm. Weekend nighttime hours were Saturday and Sunday from 10:00 pm to 11:59 pm, and from 12:00 am to 8:59 am plus Friday night from 10:00 pm to 11:59 pm, and Monday morning from 12:00 am to 7:59 am.” (Page 7, Lines 19-22, Page 8, Lines 1-4)

3.10 “Urinary tract infection was the only condition associated with the highest mortality for admissions during weekday office hours (5.5% (95% CI 4.5-6.5%)).” Please supply the mortality rates for the non-weekday office hours in the text for immediate comparison and include the p values for the difference. Please supply the p value for the difference in mortality for stroke and anemia (page 15, line 43-52).

Reply: For the discussion on p-values, please see reply 3.4.

We have revised the text. Instead of referring to the absolute number, we now refer to the table providing all numbers, which allows comparison as suggested by the reviewer. (Page 17, Lines 15)

3.11 It would be very interesting to compare the referral diagnosis to the discharge diagnosis but I realize that this is outside the scope of this paper.

Reply: It would be interesting, but we do not have the referral diagnosis in the DNRP and we do not have any information from primary care about symptoms or complaints.

3.12 “We computed length of hospital stay as time from the index date to final hospital discharge, including in-hospital and inter-hospital transfers, except those occurring more than one day after a preceding discharge as they were considered readmissions rather than transfers”. I would delete “except those occurring more than one day after a preceding discharge as they were considered readmissions rather than transfers” as it should be clear that a discharged patient that is admitted to another hospital with a time interval interspersed is a readmission.

Reply: We have revised the manuscript as suggested by the reviewer. (Page 9, Lines 17-18)

3.13 In your discussion (key findings) you refer to the highest mortality rates being for weekend admissions for the majority of the conditions examined, again, I don't think that there is a statistically significant difference. Same section you describe that "the proportion of patients arriving through the emergency room changed dramatically from weekday office hours to weekday off hours". This is a function of the organization of the health care system and is very unlikely to be a patient population characteristic.

Reply: Please see reply 3.4 for the discussion of the statistical significance of our results.

In the Methods section, we have described the key role of primary care. Primary care is also available outside office hours but the personal general practitioner is not and this may affect the behavior of the patients.[8,9] The observed pattern may be a function of the health care organization, but we believe it is worth describing.

Interpretation:

3.14 • "the overall reasons for admissions changed from office hours to off hours and weekend hours." I am not convinced about this. The admissions rates changed but did the reasons, i.e. chief complaint or admissions diagnosis change? Fewer patients were admitted during off hours

Reply: We have revised the manuscript to clarify that the main observation was a change in admission rates. (Page 21, Lines 5-8)

3.15 • "in conclusion, timing of first time admissions varied and weekend admissions were associated with the highest mortality for the majority of the conditions examined". Yes, but not statistically significant unless as an aggregate. As I read the paper, I think that the conclusion is that fewer patients are admitted during off-hours, and that they, based on their higher ICU admission rates, longer lengths of stays are sicker than the patients being admitted during the office hours.

Reply: We agree with the reviewer and have revised the conclusion in the abstract and the "interpretation" section in the discussion to clarify our view.

(Page 3, Lines 5-7) and (Page 21, Lines 4-17)

References

1. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS Med.* 2007;4(10):e296.
2. Ylijoki-Sorensen S, Sajantila A, Lalu K, Boggild H, Boldsen JL, Boel LW. Coding ill-defined and unknown cause of death is 13 times more frequent in denmark than in finland. *Forensic Sci Int.* 2014;244C:289-294.
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4. McCarthy ML, Zeger SL, Ding R, Aronsky D, Hoot NR, Kelen GD. The challenge of predicting demand for emergency department services. *Acad Emerg Med.* 2008;15(4):337-346.
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VERSION 2 – REVIEW

REVIEWER	Chris Isles Education Centre Dumfries Royal Infirmary Dumfries DG1 4AP Scotland UK
REVIEW RETURNED	15-Dec-2014.3..ZA

GENERAL COMMENTS	The authors have made considerable improvements to their paper which continues to read nicely. They have chosen not to apply statistical tests to their descriptive table on the grounds that this is not required by STROBE statements. I am not a statistician but still feel it would help to do something to this table to help readers understand whether the people being admitted at different times of day and different days of the week were in any way different. We used a chi square test in our EMJ paper which we thought was helpful. If the authors remain unwilling to consider this then may I suggest the editors ask someone who knows more about statistics than I do to have the casting vote. I am happy to defer to an expert on this point!
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REVIEWER	Deepak Bhonagiri University of New South Wales and Liverpool Hospital, Australia
REVIEW RETURNED	28-Dec-2014

GENERAL COMMENTS	I would like to see a statement in the conclusion that states that the increased mortality during weekends can be accounted for by severity of illness as measured by need for ICU admission
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VERSION 2 – AUTHOR RESPONSE

Reviewer Name Chris Isles
Institution and Country Education Centre:
Dumfries Royal Infirmary
Dumfries DG1 4AP
Scotland UK
Please state any competing interests or state 'None declared': None

The authors have made considerable improvements to their paper which continues to read nicely.

They have chosen not to apply statistical tests to their descriptive table on the grounds that this is not required by STROBE statements. I am not a statistician but still feel it would help to do something to this table to help readers understand whether the people being admitted at different times of day and different days of the week were in any way different. We used a chi square test in our EMJ paper which we thought was helpful. If the authors remain unwilling to consider this then may I suggest the editors ask someone who knows more about statistics than I do to have the casting vote. I am happy to defer to an expert on this point!

Reply:

We have carefully considered the comments from the reviewer. However, we still believe statistical

testing of differences in characteristics may not be appropriate with reference to the STROBE statements. 1 It does not say if confounding is present. In Rothman et al. *Modern Epidemiology*, 3rd edition, page 216 it is emphasized not to include p-values in descriptive tables or any other statistics designed for making inference beyond the data. The use of p-values is also covered in "The Uniform Requirements for Manuscripts Submitted to Biomedical Journals". This paper argues that one should "Avoid relying solely on statistical hypothesis testing, such as the use of P values, which fails to convey important quantitative information".

We therefore prefer to leave out p-values in the descriptive tables unless required by the Editor.2

Reviewer Name Deepak Bhonagiri

Institution and Country University of New South Wales and Liverpool Hospital, Australia

Please state any competing interests or state 'None declared': None

I would like to see a statement in the conclusion that states that the increased mortality during weekends can be accounted for by severity of illness as measured by need for ICU admission

Reply:

We agree, the conclusion of the paper is now made in concordance with the conclusion of the abstract and the statement required by the reviewer.

The conclusion now reads as follows:

"While admission rates decreased from office hours to weekend hours, there was an observed increase in mortality rates when comparing admission during weekend hours with admission during office hours. This may be explained by differences in severity of illness as measured by the need for ICU admission." (Page 23, Line 15-18)

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2. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med.* 1997;336(4):309-316.