

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is adequate pain relief and time to analgesia associated with emergency department length of stay? A retrospective study.
AUTHORS	Sokoloff, Catalina; Daoust, Raoul; Paquet, Jean; Chauny, Jean-Marc

VERSION 1 - REVIEW

REVIEWER	Brian H. Nathanson, PhD OptiStatim, LLC USA
REVIEW RETURNED	08-Nov-2013

GENERAL COMMENTS	<p>The authors are to be congratulated for taking on an interesting, important and novel study of pain management in the ED. My main concerns are as follows:</p> <ol style="list-style-type: none">1. The biggest concern is the multivariate modeling. This is the most important part of the statistical analysis and is done in a naive way. Your outcome (Length of Stay (LOS)) is skewed and cannot be negative. A linear regression model, even with a log transform, allows for negative predicted (Y) values. Furthermore, unless you use a smearing estimate (eg, Duan's Smearing), you can't easily interpret the predicted results correctly. There are more sophisticated GLM models that can better handle LOS outcome than what you have used and so the modeling should be re-done (see below for a reference). Austin, Peter C., Deanna M. Rothwell, and Jack V. Tu. "A comparison of statistical modeling strategies for analyzing length of stay after CABG surgery." <i>Health Services and Outcomes Research Methodology</i> 3.2 (2002): 107-133.<p>Alternatively, as you are presenting your results in the figures as medians, you can also consider quantile (ie, median) regression.</p><p>Finally, I can't tell how the estimated (predicted) values (page 9, 1.2 hours and 1.1 hours) were derived. Were these marginal effects or the coefficients (re-transformed) from the model? This needs to be stated more clearly and 95% CIs should be given here with specific p-values.</p><ol style="list-style-type: none">2. For the tables, it would be more helpful to put the actual IQR values (the 25th and 75th percentiles, rather than their difference) when the IQR is given.3. I think there are many places for unmeasured confounding in the study which can seriously weaken your results. You did not seem to adjust for the type or dosing level of the pain medication. Do you think that matters? I would think dosing levels would make a difference. Can you comment here. Also, have you considered
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	<p>looking at the actual level of pain (a 6, 7, 8, 9, or 10) that the patients had as a predictor of outcome. In other words, does your outcome vary in the patients at a level of 6 versus a 10?</p> <p>The paper is interesting, but there are many missing confounders and the analysis was weak (plus the sample size is modest and from a single institution). These are serious shortcoming which the authors may not be able to address.</p>
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REVIEWER	Dr M Mohsin UNSW, Australia
REVIEW RETURNED	18-Dec-2013

GENERAL COMMENTS	<p>Overall the results are expected that those who have early analgesia administration will have early cure and will have shorter LOS. However, this study needs some additional analyses which has been mentioned below.</p> <p>Specific comments:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Data analysis - The authors used Multiple Linear Regression – considered LOS as dependent variable and included a combination of both continuous (may or may not be linear) and dichotomous (non-linear Yes/No) variables. A number of explanatory variables may highly correlated e.g. triage priority (high/low), Oxygen support (yes/ no), isolation (yes/no), arrived in ambulance etc. Another set of variables Trauma injury (yes/no) and abdominal pain (yes/no) might be correlated. Inclusion of highly correlated variables i.e. multi-co-linearity affects the outcome of linear regression that need to be addressed either by excluding highly correlated variables or only including the most important one. <input type="checkbox"/> In Table 2 & 3: The Length of stay (LOS) needs to be examined by controlling for ‘route of analgesia administration’ for all the factors included. <input type="checkbox"/> In Table 2 & 3 – for continuous confounders the value range specially for ‘number of exams’ ‘number of specialist consultation’ need to be mention in bracket e.g.. Number of exams (0, 1,2, ..10) etc. <input type="checkbox"/> A cross-tabulation for ‘Time intervals (in 3-4 time interval category) between arrival and analgesia administration’ by ‘length of stay for discharged/admitted patients’ controlling by ‘route of analgesia administration’ is important to examine the impact of early or late analgesia administration. Otherwise from existing results presented in Table & 3 it is difficult for reader or policy makers to judge ‘how much length is shorter or what are the accepted delay to administer analgesia for IV/Other. Instead of median time (90 mins is too long for many severe patients) 3-4 time interval category will give better explanation to support the conclusion/hypothesis. <input type="checkbox"/> How many patients had trauma injury, blood test, heart monitoring, oxygen support, isolated need to be included in patient characteristics Table 1 or in text. <input type="checkbox"/> How the overcrowding has been mentioned it is not clear - as the staff and patient ratio differ by shift and days of the week - also shift of arrival has not been mentioned that might raise the question the about the outcomes associated with crowding. <p>Other minor comments:</p>
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	<ul style="list-style-type: none"> □ Through-out the documents (including tables) 'route of administration' – should be replaced by 'route of analgesia administration' □ In Tables 1 to 3: left column '% Arrival – ambulance, standing' – as the 'standing' is not self -explanatory to the readers - this need to be replaced by more appropriate word e.g. Ambulance (including air ambulance), other mode of transport (including foot). □ Page 7, Results – 1st paragraph "Of these patients, about 50% were male, 2/3 arrived on foot, 1,186 (58.3%) were finally discharged, and 847 were admitted". "2/3 arrived" need to be replaced by actual '%' or "two third". Also in table 1 shows 51% male whereas in text it says 50% were male that's need to be corrected. □ What does Interquartile range means need to explain at the bottom of the table 1 or in data analysis section
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. The biggest concern is the multivariate modeling. This is the most important part of the statistical analysis and is done in a naive way. Your outcome (Length of Stay (LOS)) is skewed and cannot be negative. A linear regression model, even with a log transform, allows for negative predicted (Y) values. Furthermore, unless you use a smearing estimate (eg, Duan's Smearing), you can't easily interpret the predicted results correctly. There are more sophisticated GLM models that can better handle LOS outcome than what you have used and so the modeling should be re-done (see below for a reference).

Austin, Peter C., Deanna M. Rothwell, and Jack V. Tu. "A comparison of statistical modeling strategies for analyzing length of stay after CABG surgery." *Health Services and Outcomes Research Methodology* 3.2 (2002): 107-133.

Response: Done. Generalized linear model with Gamma distribution and a log link function is now used in replacement of multiple linear regressions. We changed data analysis section of the manuscript "To examine the relative influence of adequate pain relief and time to analgesia on LOS, generalized linear model regression with Gamma distribution and a log link function was undertaken" "Generalized linear model was chosen because LOS is largely skewed and tends to produce less prediction errors than traditional linear regression (Austin et al, 2002). Mean LOS difference and Wald 95% CI adjusted at mean covariates were produced from estimated marginal means."

Finally, I can't tell how the estimated (predicted) values (page 9, 1.2 hours and 1.1 hours) were derived. Were these marginal effects or the coefficients (re-transformed) from the model? This need to be stated more clearly and 95% CIs should be given here with specific p-values.

Response: Done. Mean LOS difference and Wald 95% CI adjusted at mean covariate is now presented from estimated marginal means of GENLIN SPSS.

2. For the tables, it would be more helpful to put the actual IQR values (the 25th and 75th percentiles, rather than their difference) when the IQR is given.

Response: Done and changed in tables 1 to 4 and throughout the manuscript.

3. I think there are many places for unmeasured confounding in the study which can seriously weaken your results. You did not seem to adjust for the type or dosing level of the pain medication. Do you think that matters? I would think dosing levels would make a difference. Can you comment here? Also, have you considered looking at the actual level of pain (a 6, 7, 8, 9, or 10) that the patients had as a predictor of outcome. In other words, does your outcome vary in the patients at a level of 6 versus a 10?

Response: Type of medication was not included as confounding factor in regressions because it is mingled in the factor route of analgesia administration: opiates are generally administered IV and non-opiates are more oral or subcutaneous. Number of dose and baseline pain score are now included as confounding variables in tables 3 and 4 and in the generalized linear model regressions.

Reviewer #2

- Data analysis - The authors used Multiple Linear Regression – considered LOS as dependent variable and included a combination of both continuous (may or may not be linear) and dichotomous (non-linear Yes/No) variables. A number of explanatory variables may highly correlate e.g. triage priority (high/low), Oxygen support (yes/ no), isolation (yes/no), arrived in ambulance etc. Another set of variables Trauma injury (yes/no) and abdominal pain (yes/no) might be correlated. Inclusion of highly correlated variables i.e. multi-co-linearity affects the outcome of linear regression that need to be addressed either by excluding highly correlated variables or only including the most important one.

Response: Done. Diagnostic of multicollinearity of the regressions revealed that Variance Inflation Factor (VIF) was not high (less than 1.4 for all variables). That statistics provide confidence that the variables included in the model are not too highly correlated with each other.

- In Table 2 & 3: The Length of stay (LOS) needs to be examined by controlling for 'route of analgesia administration' for all the factors included.

Response: Done. LOS in table 2 to 4 is now separated for IV and with other than IV route of analgesia administration.

- In Table 2 & 3 – for continuous confounders the value range specially for 'number of exams' 'number of specialist consultation' need to be mention in bracket e.g.. Number of exams (0, 1,2, ..10) etc.

Response: Done. Range for these variables is now provided in table 3 and 4.

- A cross-tabulation for 'Time intervals (in 3-4 time interval category) between arrival and analgesia administration' by 'length of stay for discharged/admitted patients' controlling by 'route of analgesia administration' is important to examine the impact of early or late analgesia administration. Otherwise from existing results presented in Table & 3 it is difficult for reader or policy makers to judge 'how much length is shorter or what are the accepted delay to administer analgesia for IV/Other. Instead of median time (90 mins is too long for many severe patients) 3-4 time interval category will give better explanation to support the conclusion/hypothesis.

Response: Done. A new table (4) has been created to include LOS according to three category of delay to receive analgesia (<1 hour; between 1 and 2 hour; >2 hour delay).

- How many patients had trauma injury, blood test, heart monitoring, oxygen support, isolated need to be included in patient characteristics Table 1 or in text.

Response: Done and included in table 1.

- How the overcrowding has been mentioned it is not clear - as the staff and patient ratio differ by shift and days of the week - also shift of arrival has not been mentioned that might raise the question the about the outcomes associated with crowding.

Response: Done. A new variable created from a database of 162 000 patients of 18 years or older assigned to a bed between March 2008 and February 2011 from the same ED that select hours of arrival with high LOS and hours of arrival with low LOS is now incorporated in the confounders in tables 3 and 4 and in the regressions. That variable integrates staff and patient ratio, specialist accessibility and other factors known to affect LOS.

Other minor comments:

- Through-out the documents (including tables) 'route of administration' – should be replaced by 'route of analgesia administration'

Response: Done throughout the manuscript.

- In Tables 1 to 3: left column '% Arrival – ambulance, standing' – as the 'standing' is not self - explanatory to the readers - this need to be replaced by more appropriate word e.g. Ambulance (including air ambulance), other mode of transport (including foot).

Response: Done. Standing was replaced with "walk in" throughout the manuscript.

- Page 7, Results – 1st paragraph "Of these patients, about 50% were male, 2/3 arrived on foot, 1,186 (58.3%) were finally discharged, and 847 were admitted". "2/3 arrived" need to be replaced by actual '%' or "two third". Also in table 1 shows 51% male whereas in text it says 50% were male that's need to be corrected.

Response: Done.

- What does Interquartile range means need to explain at the bottom of the table 1 or in data analysis section?

Response: Done. As requested by the first reviewer, interquartile range is now replaced by the 25th-75th percentiles throughout the manuscript.

VERSION 2 – REVIEW

REVIEWER	Brian H. Nathanson, PhD OptiStatim, LLC USA
REVIEW RETURNED	28-Jan-2014

GENERAL COMMENTS	<p>I think the paper is much improved. The one addition that I would add would be 95% CIs for the results. The authors say there is a 2 hour difference in LOS and that the difference is significant, but it would be better to state the 95% CIs in the text and/or abstract.</p> <p>Other than adding 95% CIs to the results throughout the text, I think the paper is ready to be published.</p>
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VERSION 2 – AUTHOR RESPONSE

1. The bar charts should be replaced with tables. The data cannot be read from these diagrams.

Response : Done, we deleted the figures and added a table.

2. Please add the study design to the title.

Response : Done

3. Please be careful about using the language of causality (such as 'impact' in the title, or 'influence' in the abstract). Arguably a study design of this sort doesn't support that.

Response : Done, we changed the title to "Is adequate pain relief and time to analgesia associated with emergency department length of stay? A retrospective study." And we changed "influence" to "association".

4. Please state any competing interests or state 'None declared': None Declared

Response : Done

5. I think the paper is much improved. The one addition that I would add would be 95% CIs for the results. The authors say there is a 2 hour difference in LOS and that the difference is significant, but it would be better to state the 95% CIs in the text and/or abstract. Other than adding 95% CIs to the results throughout the text, I think the paper is ready to be published.

Response : Done, we added 95%CI in the text and abstract.