Author's response to reviews

Title: Clinical Characteristics and Outcomes of Patients with Acute Myelogenous Leukemia Admitted to Intensive Care: A Case-Control Study

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Author's response to reviews: see over
Dear Professor Norton,

Re: Manuscript Submission titled “Clinical Characteristics and Outcomes of Patients with Acute Myelogenous Leukemia (AML) Admitted to Intensive Care: A Case-Control Study” (MS ID 1552851702365376)

Thank you for the opportunity to revise and resubmit our manuscript. As you will see, we have responded and addressed each of the Reviewer’s comments from your letter dated July 2, 2010. We have made considerable revisions to the manuscript and believe these changes have strengthened the manuscript (changes are highlighted in yellow).

Response to Reviewer 1 Comments:

1. Park HJ et al (Leuk Lymphoma 2008;49(10):1929–34) could demonstrate the status of the leukemia (relapsed / refractory versus other) being an independent adverse risk factor in AML patients admitted to ICU with septic shock, among the SOFA score. This possible influence of the remission status should also be evaluated in this manuscript. Considering the median hospital stay of 35 days in this cohort, a substantial percentage of patients might have had a response evaluation before ICU admission.

We have now examined, in addition to SOFA score, the AML status of patients at the time of ICU admission. We also now integrate the paper by Park et al in our manuscript.

In addition, neutropenia and the estimated duration of neutropenia is an established risk factor for surviving infectious complications in AML. It therefore seems required to know whether both a severe neutropenia at the time of ICU admission and a prolonged neutropenia after ICU admission (>7 days) had an influence on the outcome of this cohort. Alternatively to the latter analysis, one could analyse to time from start of induction therapy to ICU admission if the AML patients were treated comparably intensive.

These are excellent suggestions by the Reviewer. We have now analyzed and included both time from AML diagnosis/induction chemotherapy and presence/duration of neutropenia associated with ICU admission and outcome.

The patients of the AML ICU and the AML non-ICU groups were not matched according to specific treatment. As the authors discuss, there is an inevitable potential bias in non-ICU patients who were precluded to ICU admission. How was the distribution of different therapeutic regimens in this patients, i.e. intensive induction therapy vs palliative cytoreductive therapy vs supportive care? If differences exist, patients of the AML-ICU and the AML-non-ICU group have to be matched according to the type of treatment.
This is an important issue raised by the Reviewer. We have reviewed our extracted data and now included in Table 2 a summary of the treatment regimen received by AML cases and controls. We did not “re-match” our AML control cohort on this variable, as we found no statistical difference between the AML cases and AML controls (p=0.60) by treatment regimen. We do recognize this as a potential limitation and have acknowledged this in the Discussion section on the paragraph on limitations.

Minor essential revisions:
p. 9: 2nd paragraph: '....ICU controls when compared with either AML cases or controls' change to: '....ICU controls when compared with either AML ICU cases or AML non-ICU cases'
This has been corrected.

table 4: the comparison of G-CSF application and application of AML-specific chemotherapy during ICU does not make sense in the comparison of AML versus non-AML-patients. In addition, the correct number is 'n.a.' (not applicable) in the corresponding non-AML controls instead of '0 (0)'. In addition, to get a comparison of the incidence of chemotherapy days, transfusions, antimicrobial therapy and G-CSF use, those parameters should be compared with the AML-non ICU group.
We agree with the reviewer. In fact, we have omitted this table and summarized the relevant points in the Results section.

p15: The conclusion '...decisions about withholding life-sustaining measures in our study may have related to...' has to be taken with caution: first, except the SOFA score, none of the other parameters showed a significant difference between the patients with switch to DNR and the others. Second and more important, a possible change of the AML disease status during the ICU stay influencing the switch to DNR (i.e. reappearance of peripheral blood blasts, bone marrow assessment showing an inadequate treatment response) has not been taken into account. The conclusion should be modified accordingly.
We agree with the reviewer. We have revised the conclusion. However, we also believe the observation of higher observed mortality associated with changes to resuscitation status and treatment limitations are relevant – as these may in fact reflect the “clinical” bias of decision-maker’s perception and also reflect the inherent limitations of single-centre studies – which represent virtually all studies on this topic.

p. 11: The statement 'Tremblay et al. reported that among 163 newly diagnosed AML...' is wrong, since the study by tremblay et al. included patients with AML of all stages of the disease, including patients receiving allogeneic hematopoietic stem cell transplantation (HSCT). This should be clearly stated, since an allogeneic HSCT places the patients to a higher risk for acquiring infectious complications than an induction therapy of a newly diagnosed AML.
The manuscript mentioned above (Park et al) should be cited
We have revised this statement.
Discretionary Revisions

Procalcitonin has been established as a good predictor for the severity of an infection. Since the vast majority of AML patients admitted to ICU suffer from infectious complications, the procalcitonin level at diagnosis or after initial antimicrobial treatment might also be evaluated as a predictor for survival. An interesting idea; however, we do not have available serum PCT levels (nor is it routinely measured at our institution).

It is much easier to follow the references if the references in the manuscript and in the supplemental table had the same numbering. This has been corrected.

Key messages: The statement '...relatively few patients...' is subjective; one could also consider 11.7% of patients suffering from a life-threatening complication after therapy a relatively high portion. We have modified this Key Message.

The matching procedure of the AML-ICU group with the non-AML ICU groups included only sex, age and APACHE II-score. While the populations are well matched by disease severity, as done by the APACHE II score, it is not clear what the differences in comorbidities in table 1 say. It might be that the 'comorbidities' were the underlying disease in many cases, as AML was for the AML-ICU group. To adjust for this, one could estimate the severity of underlying diseases by a comorbidity score. Alternatively, a table with the numbers of existing comorbidities per patient could be listed. It has to be clearly stated, however, that the ICU-non-AML group is a very heterogeneous one and only limited conclusions can be drawn from a comparison with this group. We have revised and clarified the co-morbidity data further in Table 1.

The studies leading to an approval of voriconazole in the prophylaxis of invasive fungal infections during induction therapy showed an improved overall survival in patients receiving antifungal prophylaxis during induction therapy. It could be discussed that the reported incidence of ICU admissions (from an era before voriconazole prophylaxis) could be lower now with modern antifungal prophylaxis available. This is an interesting thought; however, at our institution, antifungal prophylaxis is not routinely administered unless patients develop fever with documented neutropenia and this data on voriconazole and posiconizole have yet to be integrated into routine practice.

Response to Reviewer 2 Comments:
1) Results: Given the importance of the matching process for this study, a few questions for the authors:
a) The methods describe 1:1:1 matching. Why are there 50 patients in each of the control groups and only 45 AML patients?

The discrepancy was due to 5 patients in the AML admitted to ICU group did not having any medical record available for review – so their details could not be confirmed. Therefore, we included these patients in the incidence calculation; however, omitted them...
from the details of clinical course and outcome assessment. Accordingly, we were left
with 45 AML cases to include in the study. We have revised the manuscript accordingly.

b) One of the criteria for matching the non-AML ICU patients was the patients’
sex. In Table 1, the authors report 46% of the patients in the control group were
female, when only 26.7% of the ICU AML patients were female. Could the
authors please clarify this discrepancy? While I suspect that these issues are easily
explained, they may also point to a more systematic issue with the matching process
that would require further evaluation prior to publication.
We had initially matched for age, sex and APACHE II score (for AML cases and
controls); however, the difference observed was largely due to the above “missed” AML
cases that we could not retrieve medical records for. However, we have now increased
the number of ICU controls (ratio 1:5) and this discrepancy is now appropriately
balanced.

Minor Essential Revisions:
1) Abstract: In the methods paragraph, the authors state that both control groups
are matched according to age, sex and illness severity. In the text, non-ICU
hospitalized AML controls were matched for age and sex, but not illness severity.
Please clarify.
We have now clarified this.

2) Abstract: I don’t believe that the first sentence of the Conclusions is supported
by the data presented. Since the authors do not have access to the details
regarding those AML patients who received an ICU consult but were not admitted
to the ICU, we are unsure of the exact number of patients who actually “required”
ICU support during the study period (ie decision made to withdraw care on ward
rather than admit to ICU). In addition, I can’t agree the use of the word “rare”
when describing a phenomenon that affects nearly 12% of all patients diagnosed
with AML. Granted, as a proportion of total ICU admissions, patients with AML
are rarely admitted to the ICU; however, this has more to do with the patient case
mix in that particular ICU, the number of admissions per year and the number of
patients with AML in the catchment area. Stating both values is fine, but the
authors should reword this sentence to improve clarity for the reader.
We agree with the Reviewer. We had discussed in the Discussion section in the
paragraph on limitations the potential for selection bias due to AML patients potentially
be designated “not for ICU” on the ward. In addition, we have now re-phased our
conclusions accordingly to better reflect our data.

3) Results: While this is a personal viewpoint, I would also strongly encourage
the authors to not use the term “trend” when referring to p values near but not
below 0.05 (Lang and Secic, 2008, pg 58). (First sentence in the Baseline
characteristics, physiology… paragraph and last sentence in Treatment
intensity… paragraph). It is either statistically significant or not based on the
criteria you have set a priori.
We have revised this. However, we were unable to locate the reference provided by the Reviewer above.

4) Discussion: Page 14, paragraph 2. In general, I like the concept that the authors are espousing. However, the first sentence needs to be reworded. There are a number of factors that will predict outcome for AML patients (or any other patient for that matter) prior to or at the time of ICU admission. For example, asystolic arrest. Even if the authors were referring to clinical factors related specifically to the AML (which the current wording of the sentence does not imply), my review of the current literature would not support the use of the term “probable” at this point. Softening it to “We believe…” or “It may be the case…” or “Perhaps…” would be more reasonable. The results of this study certainly add to the current understanding of prognostication, but given the limitations already identified by the authors, conclusions cannot be drawn.
We appreciate the Reviewer’s comment. We have now revised this statement to better reflect AML-specific factors.

5) Conclusion: Same concern with the first sentence of this section as outlined in the comments for the Abstract.
This has now been revised.

6) Key messages: Last bullet: I think the word ‘them’ is missing between ‘of’ and ‘survive’.
This has been corrected.

Discretionary Revisions:
1) Materials and Methods: One of the major strengths of this study is its use of controls to better understand the outcomes of AML patients admitted to the ICU. Therefore, the control groups and the process of matching are critical aspects of the study design. A few questions for the authors:

a) Realizing that the database for the AML patients only contained 386 patients, could the matching process be more inclusive than simply age and sex? For example, are there enough patients to match by cytogenic prognosis or one of the other classification systems? (especially given the presence of 5 more “unknown” cytogenics in the ICU cases and that the control group had many more M3’s than the ICU cases (7 vs 1)).
This is a good suggestion by the Reviewer. We have included data on cytogenetics and while not a priori matched based on cytogenetic profile, there was no statistical difference between AML patients admitted to ICU and those non-ICU hospitalized patients on the ward. This was in part because we did not have the cytogenetic data prior to initiation of the study. In term of WHO/FAB classification – there were no statistical differences between the groups. As such, we do not believe it feasible, given the relatively small number of cases, to attempt to further match these patients based on AML classification.
b) Is there data available on where they are in their treatment course (ie pre-treatment, pre-transplant, or post-transplant)? Even if the patients could not be matched based on this variable, the information would help the reader interpret the results.

We have now added this data to Table 2 and discuss it in the Results section.

c) For the non-AML ICU controls, I suspect that there are a large number of admissions from which to draw controls. As it stands, I am not sure that ‘apples’ are currently being compared to ‘apples’. Are there enough patients in the ICU database to match the patients more closely? (For example, tightening the APACHE II limits to +/- 2, matching on co-morbidities, etc). This would allow the reader to be more confident that the differences are in fact attributable to the AML rather than other contributing factors.

This is a good suggestion. We have now matched AML cases 1:5 with non-AML ICU controls. In addition, cases and controls are indeed matched to age (+/- 2 yrs), sex and APACHE II score (+/- 2 points) – we had stated +/- 5 for both before a priori as we were not certain of how well we would be able to match. We are not able to match co-morbidity data for 2 reasons – matching on 4 parameters becomes increasingly complex and the Charlson score were extracted by detailed chart review. For the new controls added we have relied on the data available in the MDS database (limited co-morbidity data based on APACHE II and APACHE II diagnostic codes).

If none of these is possible (I fully realize that this would involve a massive amount of work at this point), then mentioning something about the limitations of the matching process in the limitations paragraph would be appropriate.

We appreciate the comments and have genuinely attempted to address all comments where feasible. We believe we have conducted an extensive revision and hope this satisfies the Reviewer’s criticisms.

The manuscript has been reviewed and approved by all authors. The manuscript has not been previously published and is not being considered for publication elsewhere.

If there are any further questions or concerns, please contact us at your convenience. We hope the Editor’s now find our manuscript satisfactory for publication in BMC Cancer and look forward to your review.

Sincerely,

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