Author’s response to reviews

Title: Characteristics and outcome in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study

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Author’s response to reviews:

Reply to Reviewers response:

Reviewer reports:

Sangchoon Jeon (Reviewer 1): The study demonstrates importance of biochemistry factors to diagnostic a haematological or solid cancer among patients referred to the NSSC-CPP with systemic statistical analyses, but failed to show the association of non-specific symptoms with cancer due to the biased samples with severer symptoms from other chronic diseases. Since those referred patients by GP's decisions had a potential to have more chronic problems, the associations of both biochemistry and symptom factors with cancer could be underestimated. I have no major concern about statistical analyses and interpretations, but have some suggestions for minor issues.

1) In Table 1. Age groups and comorbidity groups should be considered as ordinal variables and a trend test (e.g. Cochran-Armitage Trend Test) would be more appropriate than Chi-square test.

Reply: This is a very good point. In this specific study however, where we did not know the population at the beginning of the study, we did not want to make any assumptions on trend. Therefor we chose to use the simpler Chi-square test. There could however seem to be a trend, possibly linearly why a trend test could possibly be used in a future prospective study.

It was our plan to make as simple statistics as possible in this baseline table 1, trying not to make specific assumptions about the population.
2) I don't understand why the biochemistry factors between cancer and non-cancer patients were redundantly compared both in Table 2 and 3 (Unadjusted analysis). What's the difference between two tests?

Reply: We agree with the relevant point raised by the reviewer, that part of the results in Table 2 are similar to the results in Table 3. Therefore, we are removing the biochemistry results from Table 2 as this table is merely there to point out what has happened during the investigational course. Removing this from Table 2 has meant changes in footnotes on Table 2, 3 and 4. Changes are marked with track changes.

Referral to Table 2 has been removed in manuscript Section: 3.3 The investigational course, line 221

3) Although comorbidity was not significantly different between cancer and non-cancer patients, it could be associated with non-specific symptoms and chemistry factors. The associations of non-specific symptoms and biochemistry factors in patients without a chronic condition could be different compared to those with chronic conditions.

Reply: We agree with the point raised by the reviewer. This would be very interesting to examine however not within the scope of this study due to the retrospective design, and do to a lack in power. In the prospective study, we plan to explore this potential interesting association, and this point is added to future plans in discussions. Section: 4.5 Predictors of cancer, line 332-335

4) In diagnosis analysis, pre- (prevalence) and post- test probability provide clinically more informative than odds ratio. The likelihood ratio of post-test probability against pre-test probability will provide how much the odds of the disease increase when a test is positive. Also Area under ROC curve (AUC) of multivariate model including all significant biochemistry would provide an important information to measure the discriminability of overall biochemistry factors.

Reply: Our experience is that it is easier to interpret OR than AUC and likelihood ratios. In this retrospective study we were looking to find any hint of association as the population was previously unknown. Therefore we did not find it within the scope of this study in detail to
discriminate between different biomarkers. We will however have likelihood ratios and AUC in mind when planning statistics for future prospective studies.

5) More specific description about sensitivity analysis may be necessary. In Table 4, did they run two logistic models of haematological cancer and solid cancer separately? If so, the same comparison group (i.e. non-cancer populations) was used in both models. I would suggest multinomial model with three response levels including haematological cancer, solid cancer, and non-cancer.

Reply: We see why this is not clearly defined in the manuscript. We ran to different logistic models for haematological cancer and solid cancer. Reference groups were however different. For haematological cancers the rest of the population was used as reference (non-cancer and solid cancer) and vice versa for solid cancer (hematological cancer and non-cancer). This will be elaborated in methods.

Section: 2.4 Statistics line 175-178

Rasa Ruseckaite (Reviewer 2): I would like to congratulate authors on this well-written and a very interesting piece of work. Some minor suggestions/queries are below:

1. pg. 5 Name of the Hospital needs to be clarified - New Zealand (line 103) or New Zealand (line 108).

Reply: Thank you for pointing this out, this is of course a mistake and will be corrected in the text

Front page section: Affiliations, line 9
Section: Abstract, line 31
Section: Abbreviations, line 54
Section: 2. Methods, line 108
2. It would be very interesting to know a little bit more about the data collection and how the quality of the data was ensured.

Reply: Data collection was ensured by checking both paper forms and electronic patient files, diagnoses were looked up electronic patient files and in the diagnosis register. We did not use double entering, we did however have a SOP and difficult cases were discussed amongst the study group. Results were then entered in the SOP in order to ensure the quality of the data collection.

This will try to elaborate further on this in methods.

Section: 2.3 Data collection, line 148-153

3. It is not entirely clear what is diagnose and status follow up and how these dates are defined.

Reply: As the study was a retrospective study, the term follow up might be misleading. Patients “entered” the study at first examination, retrospectively we made a “follow-up” by looking at patient data for the following year, any diagnosis given in that period were entered in the database.

In the Kaplan Meier curve risk time for those with no cancer diagnosis were calculated as time from ended work-up at the NSSC-CPP, for those patients with a cancer diagnosis risk time started at time of diagnosis.

We will of course try to clarify this in methods.

Section: 2.3 Data collection, line 143-147

Section: 2.4 Statistics, line 181-183

4. It would be good to know whether researchers are planning to collect any QOL or patient reported outcome data. This could be addressed in their future research section.
Reply: A Ph.D. Student also assigned to the NSSC-CPP has examined QOL data in some of the same patients, information about this will be added to the article and the released article from this study will be added to references.

Section: 4.6 Strengths and limitations, line 360-361

Section: References, line 521-525

5. Implications of this study and future research section could be expanded.

Reply: We agree and will try to elaborate on this in discussions.

Section: 4.6 Strengths and limitations, line 348-351