Author’s response to reviews

Title: Quantile-based Fecal Hemoglobin Concentration for Assessing Colorectal Neoplasms with 1,263,717 Taiwanese Screenees

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Author’s response to reviews:

Re: MIDM-D-18-00233, Peng et al, “Rank-based Fecal Hemoglobin Concentration for Assessing Colorectal Neoplasms with 1,263,717 Taiwanese Screenees”

Reply to Reviewer 1 (Randi Foraker, PhD):

Thank you for the opportunity to re-review this manuscript which explored associations between f-Hb and CRC. I have remaining questions regarding the rationale for this work, which were not addressed in the revision, and would appreciate clarification from the authors as follows:

Clinically, it is of interest to predict CRC, not f-Hb. What is the rationale for using diagnosis as the independent variable and f-Hb (a clinical marker) as the outcome?
Ans: The rationale for using this alternative method has been emphasized clarified in introduction section (Page 6, Line 6 to Page 8, Line 3) like the following statements:

“While quantitative measurement of f-Hb has been considered to predict colorectal neoplasia, how to deal with statistical properties of f-Hb, including skewness and ordinal feature, has not been well elucidated. The log-transformed value of f-Hb for dealing with skewness may not follow normal distribution as f-Hb behaves like a quantile-based marker, as seen in other similar biomarkers reported in previous studies [6-17]. That means that ranking the actual value of f-Hb with the quantile distribution may be more meaningful for reflecting the underlying disease status of colorectal neoplasia. It is therefore interesting to use alternative quantile-based survival models to first estimate the unadjusted and adjusted median (i.e. 50% subjects or f-Hb50) and other different percentiles of f-Hb concentration (f-Hbp) in feces across colorectal neoplasia groups by treating the ranking of f-Hb as that of survival time in the traditional survival analysis.

Another concern is that elucidating risk factors in association with the outcome of interest in conventional epidemiological study will exclude those diagnosed as having disease at baseline. More often than not, risk factors are not part of procedure related to the confirmation of disease. However, our study is based on population-based screening for CRC with FIT that measures f-Hb. Those with f-Hb larger than 100 ng/mL are defined as FIT-positive and are referred to receive colonoscopy for confirmation. If we excluded those cases CRC neoplasia at baseline, namely prevalent (first) screen, subjects for subsequent follow-up merely include those with f-Hb less than 100, risk prediction for colorectal neoplasia would be biased because of incomplete information used for elucidating the association between f-Hb and colorectal neoplasia after excluding colorectal neoplasia at baseline. Elucidating such association between f-Hb and colorectal neoplasia have to be based on all cases rather than only incident cases excluding those at baseline. Predicting the risk for colorectal neoplasia using the conventional method that treats the disease status as the outcome and f-Hb as an independent variable with adjustment for relevant factors is therefore intractable.

Therefore, we proposed Bayesian quantile-based method in two steps to cope with the concerns raised above. The first step is to estimate covariate-adjusted f-Hb50 and f-Hbp values with survival analysis. In the second step, these percentiles of f-Hb together with baseline risk of colorectal neoplasia estimated by excluding cases at baseline were further utilized with Bayesian inversion method to assess the life-time risk for colorectal neoplasia by percentile-based f-Hb”.

It is customary to exclude those with the outcome of interest at baseline so that risk can be properly assessed. Was this done? How many had the outcome of interest at baseline assessment?

Ans: Yes, the risk prediction for colorectal neoplasia has excluded prevalent (first screen) cases at baseline when Bayesian inversion method is used. However, we have to elucidate the
association between f-Hb and colorectal neoplasia to provide likelihood information using the percentiles of f-Hb before Bayesian posterior risk prediction model.

Elucidating such association between f-Hb and colorectal neoplasia have to be based on all cases rather than only incident cases excluding those at baseline. This is explained as follow. In epidemiological study, elucidating risk factors in association with the outcome of interest will exclude those diagnosed as having disease at baseline. More often than not, risk factors are not part of procedure related to the confirmation of disease. However, our study is based on population-based screening for CRC with FIT that measures f-Hb. Those with f-Hb larger than 100 ng/mL are defined as FIT-positive and are referred to receive colonoscopy for confirmation. If we excluded those cases CRC neoplasia at baseline, namely prevalent (first) screen, subjects for subsequent follow-up merely include those with f-Hb less than 100, risk prediction for colorectal neoplasia would be biased because of incomplete information used for elucidating the association between f-Hb and colorectal neoplasia after excluding colorectal neoplasia at baseline. Therefore, we used Bayesian quantile-based method in two steps to cope with this concern. This has been provided in the introduction section (Page 7, Line 1 to Line 16).

Therefore, we first elucidated the association between quantile f-Hb and colorectal neoplasia based on all data including 10,880 subjects (7,814 identified at first screen and 3,066 identified at subsequent screens) with non-advanced adenoma, 4,604 subjects (3,491 identified at first screen and 1,113 identified at subsequent screens) with advanced adenoma, 1,765 prevalent screen-detected CRC, 1,608 subsequent screen-detected CRC, and 3,247 interval CRC. Such information has been provided in the method section (Page 10, Line 15 to Page 11, Line 1).

We then applied the Bayesian inversion method to derive posterior risk prediction for colorectal neoplasia based on two parts, baseline risk for colorectal neoplasm without information on f-Hb estimated by using Poisson regression mode to incident cases by excluding colorectal neoplasia, and likelihood information with percentiles of f-Hb given disease status derived from above. This has been explained in the method section (Page 11, Line 3 to Page 12, Line 7) and also clarified in Supplementary materials (See the text of Appendix).

Please expand upon how lifetime risk of CRC can be calculated from these data. As written, and given the issues identified by the reviewer, the study methodology does not support calculation of lifetime risk of CRC.

Ans: See the reply to Q2 and also the detailed description given in Appendix shown in the following.

“First, we applied an accelerated failure time (AFT) model to our data which included information on prevalent and repeated rounds of screen to estimate the percentile of f-Hb by type
of colorectal neoplasia (denoted as Dstatus) to form likelihood function used below. We then employed a Bayesian inverse method given average values of adjusted covariates (X) used in the likelihood function and the prior of incidence of these diseases excluding disease at baseline (cases detected at prevalent screen) to estimate the risk of CRC and adenoma.

\[ P(D\text{status}|fHb,X) = \frac{P(fHb|D\text{status},X) \cdot P(D\text{status}|X)}{P(fHb,X)} \]

The estimated disease incidence (estimated by a Poisson regression model with empirical data excluding disease at baseline) would be:

\[ P(CRC|X) = \frac{96.40}{100,000} ; \quad P(\text{Adv-adenoma}|X) = \frac{53.66}{100,000} ; \quad P(\text{Nonadv-adenoma}|X) = \frac{135.34}{100,000} ; \]

where Dstatus represents disease types including CRC, advanced adenoma, and non-advanced adenoma. X were the covariates we adjusted in AFT model, including sex, age, family history of CRC, and brand of FIT.”

Reply to Reviewer 2 (Iris Lansdorp-Vogelaar):

The authors have assessed the association between fHb concentration and detection of colorectal neoplasia using a novel methodology that they claim avoids some of the bias associated with standard approaches. Although I see merit in their work, I have some major concerns with the manuscript in its current form:

The authors description of the methods and the work is not intuitive. Based on the description I would expect survival curves. Yet Figure 3 portrays cumulative percentage curves. It is not until reading the discussion that it becomes clear that indeed fHb concentration is considered as time. This intuitive explanation (bottom of page 20) should be added to the methods section.

Ans: Thank you for the reviewer’s kind suggestion. The detailed methodology using Bayesian Quantile-based f-Hb for predicting the risk of colorectal neoplasia with survival analysis combining with Bayesian inversion method has been provided in method section (Page 11, Line 3 to Page 12, Line 7). Using the concept of survival analysis, the corresponding survival curves can be shown below.

The original cumulative percentage curves shown in Figure 3 is just the complementary survival curves. This has been explained in the method section (Page 11, Line 15). We therefore kept the same cumulative curves in the revised manuscript.
I don't see the advantage of using this method over previous methods. The authors claim that rank-based methodology is needed because fHb concentration data are skewed. Is ranking ordinal fHb the only solution to the problem? The discussion says that skewedness could be easily solved using log-transformation. Can we not just use the regular risk-prediction techniques on log-transformed data that are more intuitive?

Ans: The reason for not relying on log-transformation method but using the ranking (quantile) survival method has been explained in the introduction section (Page 6, Line 7 to 19). The log-transformed values failed to follow normal distribution have been described in result section (Page 17, Line 14-16) and shown in Appendix-Figure 1 (B).

We also used the following example for explaining why log-transformation can be used to deal with skewed interval-scaled data but not for ordinal type data. Using the ordinal-based or quantile-based regression model like survival analysis may provide more accurate information on ordinal property of f-Hb.

For example, if we have one dataset as below,

<table>
<thead>
<tr>
<th>Survival time</th>
<th>X1</th>
<th>X2</th>
<th>X3</th>
<th>X4</th>
<th>X5</th>
<th>X6</th>
<th>X7</th>
<th>X8</th>
<th>X9</th>
<th>X10</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0.8</td>
<td>0.9</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>2.5</td>
<td>3.6</td>
<td>15</td>
<td>25</td>
<td>50</td>
<td>10.2</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.6</td>
<td>2.7</td>
<td>2.8</td>
<td>2.9</td>
<td>3</td>
<td>3.3</td>
<td>3.7</td>
<td>3.8</td>
<td>3.9</td>
<td>4</td>
<td>3.27</td>
</tr>
<tr>
<td>Log-transform for group1</td>
<td>0.22</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-transform for group2</td>
<td>0.96</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank of group1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>13</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>9.1</td>
</tr>
<tr>
<td>Rank of group2</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>11.9</td>
</tr>
</tbody>
</table>

There are two groups for the comparisons of survival time. Group 1 has a highly skewed survival time, while group 2 has a homogeneous survival time. After log-transformation, the mean survival time of group 1 is higher than group 2. While using the ranks of survival time of two groups, the problem of tail distribution of survival time can be ameliorated. The median survival time and the ranks in group 1 are shorter than those group2. Using the same concept, we ranked the f-Hb concentration as did for survival time for the comparison of colorectal neoplasia groups to deal with f-Hb.

Why are tail end outcomes and skewedness even a problem for unbiased estimation? How would this affect your outcomes? This should be explained more clearly in the introduction to better set the stage for the authors work.
Ans: Tail distribution of f-Hb, the extreme value of f-Hb, is related to the disease status as shown in Figure 1. The association between f-Hb and colorectal neoplasia cannot be merely based on log-transformation method but must consider the ordinal property with quantile values of f-Hb. Statistical properties of f-Hb, including skewness and ordinal feature, have been heralded in the introduction section (Page 6, Line 7-19) as suggested.

The methods are not described clearly enough. A lot of necessary information is lacking, such as definitions of who are considered neoplasm free, description of the Bayesian inversion method, how people are followed and treated in the analysis: how are people without neoplasia detected in round 1 treated if they develop neoplasia later in time. There is 1-2 sentences somewhere, but the information is too concise to get the full picture. On the other hand, the conceptual framework in the methods is very obvious and in my eyes largely redundant. It takes up a lot of space. I suggest to remove most of this framework to allow for more detailed explanation of the method plus its rationale. Some of these intuitive findings could actually be used to start of the results section.

Ans: The conceptual framework has been removed and changed into Bayesian quantile-based f-Hb for predicting the risk of colorectal neoplasia (see the method section, Page 11, Line 3 to Page 12, Line 7). The detailed formula has been also given in the text of Appendix mentioned like the following

“First, we applied an accelerated failure time (AFT) model to our data which included information on prevalent and repeated rounds of screen to estimate the percentile of f-Hb by type of colorectal neoplasia (denoted as Dstatus) to form likelihood function used below. We then employed a Bayesian inverse method given average values of adjusted covariates (X) used in the likelihood function and the prior of incidence of these diseases excluding disease at baseline (cases detected at prevalent screen) to estimate the risk of CRC and adenoma.

\[
P(Dstatus|fHb,X) = \frac{(P(fHb|Dstatus,X) \cdot P(Dstatus|X))}{P(fHb,X)}
\]

The estimated disease incidence (estimated by a Poisson regression model with empirical data excluding disease at baseline) would be:

\[
P(CRC|X)=96.40/100,000 \quad ; \quad P(Adv-adenoma|X)=53.66/100,000 \quad ; \quad P(Nonadv-adenoma|X)=135.34/100,000 \;
\]

where Dstatus represents disease types including CRC, advanced adenoma, and non-advanced adenoma. X were the covariates we adjusted in AFT model, including sex, age, family history of CRC, and brand of FIT.”
The authors performed this analysis to address bias from skewedness of the data. However, I am concerned that this method is even more prone to detection bias than the standard methodologies. All people with low fHb concentrations are classified in the "no neoplasm" group. Yet many of these individuals may actually have neoplasms. It may very well be that if these people were to be included in the correct group, that the differences in fHb concentrations between the groups would be much smaller, theoretically even non-existent. The authors can try to assess this bias by only looking at individuals that underwent colonoscopy and evaluate if they see the same rank-ordering of fHb concentrations.

Ans: The proposed Bayesian quantile-based f-Hb method by including data on prevalent (first) screen, repeated screen, and interval cancer while elucidating the association between the percentiles of f-Hb and colorectal neoplasia provides alternative solution to detection bias at prevalent screen with extreme value in the tail distribution of f-Hb and the misclassification of those with low fHb concentrations that were classified in the "no neoplasm" group at first screen but re-appear in the subsequent screen and interval cancer. The similar concern related to such a detection bias by providing all types of data instead of only incident cases has been delineated in the introduction section (Page 7, Line 1-16).

Page 12, line 49: states that interval cancers are censored. However, subsequent lines seem to suggest that missing values are imputed and so these cases are not censored, but included in the analysis. I have concerns about the imputation method: I strongly suggest to also include actual measured fHb in the imputation, because to me that seems most reliable information you have about concentration value.

Ans: Interval cancer is defined as participants with negative FIT in the updated screening, and developed as cancer with clinical symptom. So the last f-Hb concentration cannot represent the true value (it is impossible to get in population-based screening program) of interval cancer cases that when they were diagnosed as cancer, that is why we called “censored on f-Hb”. In the concept of screening program, participant with cancer should be either prevalent case detected in the first round of screening or subsequent cancer detected in subsequent round of screening. We have no choice but impute these interval cancers with censored values of f-Hb by assuming they have the same feature as the mixed of prevalent and subsequent screen-detected cancer. This has been re-written in method section (Page 15, Line 16).

Abstract: from reading the abstract, I was very unclear about the analysis performed. Also, the word rank is never used in methods, but is included in conclusion and title. Unclear what is meant by rank-based. Suggest to reformulate or include also in methods and results so that it is clear what is meant.
Ans: The title has been changed as “Quantile-based f-Hb….”. How the quantile-based method is used has been clarified throughout the text of abstract.

Table 3: risks at 90th percentile add up to >100%. Does that make sense? Can the authors explain?

Ans: The findings shown in Table 3 are posterior risk of each type of colorectal neoplasia given the percentile of f-Hb on the basis of Bayesian inversion method by combining prior (baseline risk for colorectal neoplasia) with likelihood with information on the percentile of f-Hb. That has been clarified in the method section (Page 11, Line 3 to Page 12, Line 7).

The detailed formula is also provided in Appendix section. This is delineated as follows.

“The Bayesian inversion method in our analysis was based on the estimated association of f-Hb and disease statuses using accelerated failure time model in the first step. We applied a Bayesian inverted method, given average values of adjusted covariates used in the model and incidence of these diseases excluding the disease at baseline, to estimate the risk of CRC and adenoma. The formal formula for estimating the risk is as following,

P(Dstatus|fHb,X)=(P(fHb|Dstatus,X)∙P(Dstatus|X))/P(fHb,X)

where Dstatus represents disease types including CRC, advanced adenoma, and non-advanced adenoma.”

This explains why the sum of risk at 90th percentile of f-Hb of neoplasms were not equal to 100%. The results in Table 3 are clinically reasonable. The higher the f-Hb, the higher the risk of being diagnosis as adenoma or cancer.”

Minor comments:

Figure 3: does this figure not sort of represent a sensitivity/specificity estimate? To me it is more intuitive to describe it that way.

Ans: See the reply to major comments Q 1.

Line 24: What does 83% reflect. Suggest to delete it or fully explain it.
Page 9, Line 37: Use prevalent and incident screen, or first and second round. No mix and match.

Ans: This has been provided in method section (Page 10, Line 15 to Page 11, Line 1) as follows. “Note that we elucidated the following association between quantile f-Hb and colorectal neoplasia based on all data including 10,880 subjects (7,814 identified at first screen and 3,066 identified at subsequent screens) with non-advanced adenoma, 4,604 subjects (3,491 identified at first screen and 1,113 identified at subsequent screens) with advanced adenoma, 1,765 prevalent scree-detected CRC, 1,608 subsequent screen-detected CRC, and 3,247 interval CRC.”

Suggest to drop the non-parametric model, since it does not add anything to the analysis.

Ans: Nonparametric method of survival analysis here was applied to present the unadjusted percentile of f-Hb based on the empirical data.

From the manuscript fHb concentration for different percentiles of normal individuals seem to be lacking. Why?

Ans: In our study, we are interested in predicting the risk of colorectal neoplasms instead of being free of colorectal related disease. Besides, for those free of colorectal cancer and adenoma, we could expect most of them had an extremely low value of FIT, even undetected, so it is impracticable to present the percentiles of normal colon cases. This also account for why we used survival method for ranking these values of f-Hb.