Original Article

Health-related quality of life in patients with advanced colorectal cancer: a predictive nomogram including BMI, sex and age

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Background: Health-related quality of life (HRQoL) is not universally assessed in metastatic colorectal cancer (mCRC) patients. We tried to identify patient subgroups for whom HRQoL assessment should be strongly encouraged.

Methods: Consecutive mCRC patients who had been deemed candidates for first-line chemotherapy were enrolled in a prospective study (NCT03873064) and asked to complete the HRQoL questionnaire EORTC QLQ-C30. Primary endpoint was the Global Health Status (GHS) of EORTC QLQ-C30. A nomogram was built for prediction of low GHS (i.e., <67%).

Results: Among recruited patients (n=173), a univariable logistic regression analysis (LRA) found that body mass index (BMI <23), age (>65 years) and sex (female) were significantly associated with low GHS. The multivariable LRA confirmed they were independently associated with the outcome (P values of 0.04–0.004). BMI, age and sex were included in a final predictive model (C-statistics, 67%; P=0.001) and used to build a nomogram. A total nomogram score ≥72 was associated with a risk of 28% or higher of having a low GHS. The 28% risk cut-off had a sensitivity of 90% and a specificity of 34% for identifying low GHS. A decision curve analysis revealed that a risk threshold of 28% of the model was associated to an added net benefit of ≥4% when using the nomogram. Low GHS was recorded in 58% *vs.* 23% of patients with >28% *vs.* <28% risk according to the nomogram, respectively (odds ratio 3.54, P=0.0004).

Conclusions: High BMI together with young age and male sex were protective against HRQoL deterioration. In centers where HRQoL is not routinely assessed, such an assessment should be at least made for mCRC patients at risk according to the proposed nomogram (i.e., over 65-year-old females with BMI <23).

Keywords: Metastatic colorectal cancer (mCRC); health-related quality of life (HRQoL); Global Health Score (GHS); nomogram

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Introduction

Colorectal cancer epidemiology

Colorectal cancer represents a high burden on the society worldwide, ranking as third in terms of incidence and second in terms of mortality among all cancer types. The World Health Organizations has estimated approximately 1,800,000 new diagnoses of and 860,000 new deaths from colorectal cancer worldwide in 2018 (1). The incidence/mortality ratio gives the idea that nearly half of colorectal cancers are incurable and lead to premature death. The number of subjects with a past or active diagnosis of colorectal cancer is steadily increasing, especially among elderly with relevant comorbidities, and is estimated to double in 30 years' time (2).

Quality of life in oncology and colorectal cancer

When the disease is deemed incurable, maintenance of health-related quality of life (HRQoL) and patient reported outcomes (PROs) are paramount (3). Nonetheless, reports on HRQoL measures have so far been suboptimal in the cancer literature. In a recent telephone inquiry involving nearly ten thousand subjects across seven different European countries, HRQoL was reported by 60–80% of the respondents to be even more important than extending the overall survival in the hypothetical case of a 'serious illness like cancer limiting the time to live' (4).

HRQoL is identified itself as the primary endpoint in some studies. Beside this, it has also been established, in many oncological settings (including lung, breast, colorectal, and prostate cancers), as a powerful predictive factor of other primary objectives such as overall survival (5-8). Moreover, HRQoL maintenance is a fundamental requirement for innovative therapies since toxicity-related HRQoL impairment may significantly limit their implementation, and therefore it is often set as secondary endpoint in clinical trials (9-11).

So far PROs have been mainly used for research purposes. However, more recently their importance has been recognized also for practical application in order to improve the quality of the care delivered by Healthcare Systems. Strategies to systematically record PROs and include them in routine clinical practice are now taken into consideration (12). In this regard, they can be used as intervention tools to modulate nutrition support, physical activity and physiotherapeutic strategies (13). A number of questionnaires have been developed to capture and measure HRQoL (14) with challenges still remaining about optimal patient adherence. Furthermore, lack of guidelines to help clinicians respond to issues of patient HRQoL and the cost-benefit ratio in terms of clinician workload and the overloading of health services are other matters of debate (15).

As far as HRQoL in metastatic colorectal cancer (mCRC) patients is concerned, a recent population-based reports have evidenced that this disease may be associated with a significant HRQoL burden including bowel, urinary, and sexual problems even 1–3 years after the diagnosis (16).

In centers where PRO recording is not routinely used in mCRC management, it would be at least desirable to facilitate the identification of frail mCRC patients for whom full HRQoL assessment is indispensable (17).

Obesity and quality of life in colorectal cancer patients

Obesity is a complex physiopathological state that involves significant changes in the systemic metabolic profile (18,19), circulating levels of insulin and other growth hormones (20), baseline innate immunity activation (21) and vasomotor response (22-24). Such changes pave the way for an increase in the risk of cardiovascular diseases, cancer and diabetes (25-27). Nonetheless, a possible survival advantage has been hypothesized for certain oncological settings in presence of metastatic disease, raising the possibility that an 'obesity paradox' and a protective role of high BMI would exist for some cancer patients (28,29). However, the effect of obesity on HRQoL of mCRC patients is under-reported

Aim of the study

The aim of the present study was to investigate the effect of BMI and other clinical variables on HRQoL in metastatic colorectal cancer patients treated with standard chemotherapy and generate a possible HRQoL-specific predictive score. Analyzed variables (anthropometric, sociodemographic, lifestyle, and clinical variables) are universally collected and readily available in electronic charts. The subgroup of mCRC patients identified as at risk according to the predictive score should be offered full HRQoL assessment and subsequent tailored supportive strategies in the routine clinical practice of Oncology Units.

We present the following article in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/apm-20-2194).

Methods

Study design

This is a prospective monocentric observational pilot study (TV-ONCO study, NCT03873064, local Ethics Committee Approval ID: R.S. 102/17) where consecutive adult patients referred to the Medical Oncology Unit of Tor Vergata University Hospital (Rome, Italy) with a histologically confirmed diagnosis of colorectal cancer and measurable metastatic disease were recruited. Patients who were to start a first-line chemotherapy treatment were requested, following informed written consent, to complete the EORTC-QLQ-C30 questionnaire (30), and basic information regarding sex, age, body mass index (BMI), height, level of education, marital status, alcohol and caffeine consumption and smoking habit were recorded.

Other data on socioeconomic status and working conditions were not systematically collected. They were often missing in medical records and were not included in the present analysis. First-line chemotherapy was started within 1 week of questionnaire completion. A prospectively maintained database linked to the central medical records system was used for the necessary clinical information.

The study was approved by the Local Ethics and Scientific Committees (local Ethics Committee Approval ID: R.S. 102/17) and performed in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all individual participants included in the study.

Statistical considerations

EORTC-QLQ-C30 data were managed and analysed according to the instruction manual (31). Global Health Score (GHS) was the primary objective. It was derived from the last two questions of the EORTC-QLQ-C30 and the final score for each participant was re-scaled from 0% to 100%, with higher scores indicating better HRQoL. For the purpose of the analysis, GHS was dichotomized according to its median value in the study population (high GHS, coded as 0, *vs.* low GHS, coded as 1).

No candidate predictor pre-selection was performed since the subject matter was thought to be relatively underexplored and no a priori exclusion of variables was decided.

Standard univariable and multivariable logistic regressions were performed to identify significant predictors of low GHS. Variables with a significant effect at the univariate analysis (P value <0.05) were selected for the multivariate analysis. C-statistics, Nagelkerke's R2 and the Brier score were used to provide performance measures of the multivariable predictive model.

Before running the univariate logistic regression analysis (LRA), continuous variables (age, height and BMI) were grouped into deciles and qualitatively assessed for their association to the outcome by visually inspecting smoothed frequency curves of low *vs.* high GHS ('cdplot' function of R software). When the association appeared to be not linear, the continuous variable was dichotomized with the dichotomizing value chosen based on the curve shape (see supplementary material, Figure S1).

The resulting multivariable model was internally validated with 100 bootstrap resampling. Apparent calibration of the model was assessed by analyzing the relationship between predicted risk and actual incidence of low GHS for increasing risk in the study population.

By using the variables found to be significant in the multivariate analysis, a nomogram was built to estimate the predicted risk of suffering from low GHS.

Risk cut-offs identified thanks to the nomogram were analysed by means of receiver operating characteristic (ROC) curve analysis to determine sensitivity and specificity for low GHS prediction.

The clinical usefulness of the model was assessed by means of decision curve analysis to determine the net benefit of using the model for low GHS patient identification (32).

All analyses were performed with R software version 3.5.1. All tests were considered statistically significant for two tail P values <0.05.

Results

Between January 2015 and November 2018, 181 patients with mCRC were invited to participate in the study, of whom 173 returned the EORTC QLQ-C30 having completed questions 29 and 30, i.e., the Global Health Score (GHS), with a compliance rate of 96%. Patients' characteristics are presented in *Table 1*.

For the purpose of the analysis, GHS was dichotomized-based on the median value of 67%, in high GHS (≥67%, coded as 0) and low GHS (<67%, coded as 1).

For the univariate LRA for GHS prediction the following variables were included: age, education level (primary school coded as 1, higher educational stages coded as 0), height, BMI, marital status (single coded as 1, married or

Table 1 Characteristics of the 173 enrolled patients. In parentheses the percentage within the group except when otherwise specified

Category	Outcome
Gender	
Male	104 [60]
Female	69 [40]
Age (years)	65 [44–88]
Height (cm)	168 [145–195]
BMI (kg/m^2)	25 [14–36]
Time since initial diagnosis (kg/m^2)	6 [1–57]
Planned chemotherapy	
Chemo+ anti-VEGF	78 [45]
Chemo+ anti-EGFR	60 [35]
Chemo alone	35 [20]
Civil status	
United	130 [75]
Single	43 [25]
Education	
Primary school	34 [20]
> Primary school	139 [80]
Principal caregiver	
Spouse	77 [45]
Others	96 [55]
Coffee cups (day)	
0 to 2	161 [93]
3 or more	12 [7]
Regular alcohol use	
No	152 [88]
Yes	21 [12]
Smoking habit	
Never	91 [53]
Current/former	82 [47]
Global Health Score (%)	67 [0–100]

Data are shown as median [range] or number [%].

living with a partner coded as 0), principal caregiver (spouse coded as 0, others coded as 1), consumption of coffee cups a day (<3 coded as 1, 3 or more coded as 0) , alcohol use (yes coded as 1, no coded as 0), smoking habit (current/former coded as 1, never coded as 0).

Before running the univariate LRA, continuous variables (i.e., age, height and BMI) were grouped into deciles and qualitatively assessed for their association to the outcome by visually inspecting smoothed frequency curves of low *vs.* high GHS by using the 'cdplot' function of R software (Figure S1).

By inspecting the frequency plots, a higher occurrence of low GHS was seen for the 6th to 10th decile of age (age >65 years) and for the 1st to 3rd decile of BMI (BMI ≤23). Therefore, the age variable was dichotomized <65 years (coded as 0) *vs.* >65 years (coded as 1), and the BMI variable was dichotomized ≤23 (coded as 1) *vs.* BMI >23 (coded as 0). Height was found to be linearly associated with GHS and therefore kept as a continuous variable.

At the univariate LRA, sex, age and BMI demonstrated a significant association (P<0.05) to GHS (*Table 2*) and were used for the multivariable LRA.

Multivariable LRA showed that the three variables retained a significant association with GHS (P values from 0.04 to 0.004, *Table 3*) and a full predictive model including age, BMI and sex was built, that produced a C-statistics of 67%, a Nagelkerke's R2 index of 12% and a Brier score of 0.228, P=0.001. Coefficients of the single variables of the full model are reported in *Table 3*.

Apparent consistency and performance of the model was good, as demonstrated by a calibration analysis of predicted *vs.* actual probability of having low GHS (Figure S2).

Internal validation was carried out with a set of 100 bootstrap resample. Bootstrap resampling provided a corrected mean Nagelkerke's R2 index of 11%, and C-statistics of 65%, slightly inferior to the original values.

The three variables were used to generate a nomogram with the following scoring system: BMI ≤23 =77 points, females =72 points, age >65 years =100 points (*Figure 1*).

According to the nomogram, a total score ≥72 (presence of at least one of the three risk factors) was associated with a predicted risk >28% of having a low GHS. Female patients

Table 2 Univariate logistic regression analysis for Global Health Score prediction

Variable	Coef.	S.E.	LR chi2	P(> chi2)
Gender (female *vs.* male)	–0.6132	0.3148	3.85	0.0499
Age (<65 *vs.* >65 years)	0.7732	0.3099	6.34	0.0118
Height (cm) (continuous variable)	–0.0242	0.0170	2.07	0.1500
BMI (>23 *vs.* ≤23 kg/m^2)	0.6719	0.3300	4.23	0.0397
Civil status (united *vs.* single)	0.6774	0.3612	3.61	0.0574
Education (primary school *vs.* higher education)	0.5804	0.3917	2.25	0.1339
Caregiver (spouse *vs.* others)	0.4968	0.3085	2.61	0.1059
Coffee cups/day (<3 *vs.* 3 or more)	1.1856	0.6851	3.44	0.0637
Alcohol consumption (yes *vs.* no)	–0.1216	0.4661	0.07	0.7940
Smoke (yes *vs.* no)	–0.2076	0.3049	0.46	0.4956

Table 3 Coefficients of the individual variables included in the full multivariable model

Variable	Coef.	S.E.	P(> chi2)
Gender (female *vs.* male)	–0.6647	0.3296	0.0437
Age (<65 *vs.* >65 years)	0.9236	0.3247	0.0044
BMI (>23 *vs.* ≤23 kg/m^2)	0.7075	0.3431	0.0392

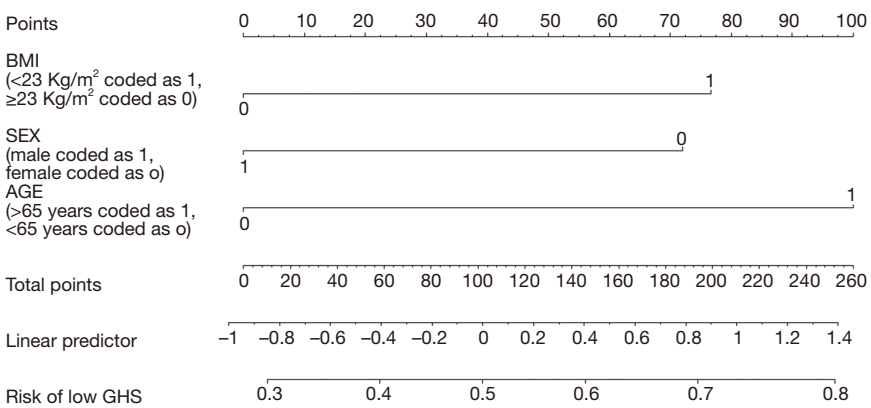

Figure 1 Nomogram based on age, gender and BMI to predict poor quality of life of metastatic colorectal cancer patients approaching a first-line chemotherapy. Poor quality of life was defined as a Global Health Score (GHS) of the EORTC-QLQ-C30 questionnaire <67%. The scoring system was as follows: BMI ≤23 kg/m^2 =77 points, female gender =72 points, age >65 years =100 points. Absence of the aforementioned risk factors returned score 0. A total score of 72 or more (at least one risk factor present) was associated with a risk >28% of having a poor GHS.

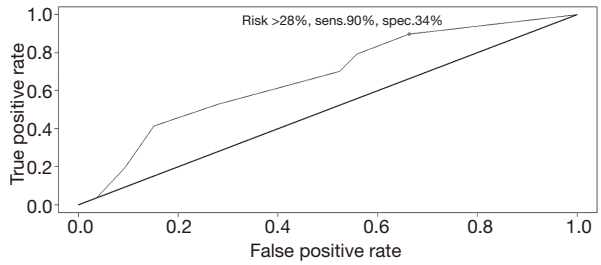

Figure 2 Receiver operating characteristic (ROC) curve analysis for increasing risk thresholds of poor Global Health Score based on the generated predictive nomogram. A predicted risk >28% was associated with a sensitivity of 90% and specificity of 34%.

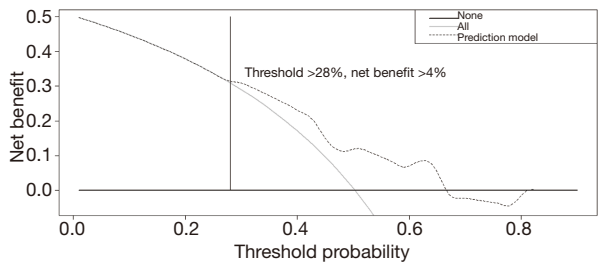

Figure 3 Decision curve analysis when using the predictive nomogram for poor Global Health Score (GHS). According to the decision curve analysis, for nomogram-derived risk thresholds superior to 28% the net benefit of the nomogram-based approach (dashed line) exceeded the net benefit of 'including all-patients' approach (grey line). The net benefit for thresholds >28% was >4%. Black line represents the 'including none' decision.

with a BMI ≤23 and older than 65 years (all three risk factors present) had a predicted risk of 79% of reporting low GHS.

A ROC curve analysis was performed to define the sensitivity and specificity of the 28% risk threshold.

The nomogram-derived 28% risk cut-off was associated with a sensitivity of 90% and a specificity of 34% (*Figure 2*).

In the study population, patients with a predicted risk >28% had an actual prevalence of low GHS of 58% as compared to 23% of patients with a predicted risk of ≤28%, (odds ratio 3.54, P<0.0004). The actual prevalence of low GHS among patients with all three factors was 74%.

To determine the net benefit of using the generated nomogram to select patients in greater need of full HRQoL evaluation and appropriate supportive care strategies, a decision curve analysis was performed (*Figure 3*). By using the 28% risk threshold, there was an added net benefit of ≥4% of patients adequately identified as low GHS patients as compared to the 'including all' policy.

Discussion

In the present pilot study, we set up a quality of life nomogram using simple and readily available variables at baseline. The nomogram had the objective of increasing the awareness on mCRC patient features at risk of deteriorated quality of life. Even though HRQoL is widely recognized as an important outcome to take into consideration, it is not yet broadly and routinely measured in Oncology Units and clinical instruments predicting HRQoL have seldom been implemented in daily practice (33,34).

Assessment of HRQoL should represent a crucial aspect in the decision-making process as the most 'patient-centric' parameter, however it is often neglected in routine practice even if it does not require particular facilities or devices.

To the best of our knowledge, this is the first quality of life nomogram specifically built for patients with mCRC candidate for a first-line chemotherapy. Using nomograms may, at times, be laborious and time-consuming, however the availability of specific apps on mobile devices or tablets has significantly improved this process. Nevertheless, our nomogram is quite simple and easy to apply. It is based on dichotomized variables and the final output can be summarized by stating that the presence of at least one of three possible risk factors (female sex, age >65 years or BMI ≤23) puts the patient at risk of poor HRQoL. The AUC (67%) and the added net benefit at a risk cutoff of 28% (4%) should be regarded as sub-optimal, however the main intent of the nomogram is to rapidly screen patients who would need a second-level evaluation with minimization of the risk of missing true positive cases. The sensitivity of the model was indeed as high as 90%.

The clinical relevance and practical usefulness of the nomogram is linked to the fact that in many centers HRQoL assessment is not universally carried out during the initial patient consultation, whilst it is an issue that may arise later after treatment start. Information regarding sex, BMI and age are universally available in medical records, and, based on our nomogram, can be rapidly used to identify mCRC patients for whom full HRQoL assessment should be considered indispensable. The nomogram might possibly be incorporated into electronic medical records with automatic warning signal to prompt HRQoL questionnaire administration. The 'on-treatment' monitoring of HRQoL was beyond the scope of the present study, however the authors recognize that it is another area of clinical interest, which warrants specific study designs.

A recently reported population-based HRQoL

assessment at 12 to 36 months of colorectal cancer diagnosis, revealed that as many as 65% of patients reported one or more HRQoL problems (16). In this report, which included more than 20000 patients (including both metastatic patients and patients with localized disease), advanced age (>85 years) and female sex were confirmed to be poor HRQoL predictors, with results comparable to those found in our cohort. BMI was not investigated.

In another study by Gray *et al.*, nearly 500 colorectal cancer patients with either localized or advanced disease were asked to complete the EORTC-QLQ-C30. Female sex was found to be significantly associated with the global health status (P<0.001), but, taken on its own, had little correlation with the outcome in a multiple linear correlation model (correlation coefficient R2 =0.064). No integrated model was built in this study (35).

The impact of age and sex on HRQoL was also demonstrated in other cancer settings (36), while the impact of BMI on quality of life is under-reported. In mCRC patients low BMI is associated with sarcopenia and poorer clinical condition, and this is the probable explanation of the low HRQoL found for BMI <23 in our cohort (37-39).

Lis *et al.* looked at the association between nutritional status, BMI and HRQoL across different cancer types in a systematic review. Twenty-four studies were selected with the majority being on gastrointestinal cancer (8 studies). Poor nutritional status (which was associated with sarcopenia and low BMI) was confirmed to be a strong predictor of poor HRQoL in patients with cancer (40).

BMI, sex and age have also been used, together with other socio-economic, lifestyle and treatment-related factors, to predict quality of life in colorectal cancer survivors long after the diagnosis (~5–6 years after the initial diagnosis) (41).

In our study, patients were approached either in the outpatient clinic before the visit or at the moment of the hospital admission, and the close interaction with Health professionals in the period immediately after questionnaire administration yielded an impressively high response rate (96%), thus minimizing non-response bias (42). The nomogram we built included variables all independently associated with poor HRQoL (age >65 years, female sex and BMI <23 kg/m^2). The presence of at least one of the three risk factors was associated with a predicted risk of poor HRQoL >28% and selection of patients according to this criterion was sufficient to provide a net benefit superior to an 'all-inclusive' policy when deciding who requires full HRQoL assessment.

A major drawback of our study is the absence of external validation, however the homogeneity of the patient group (all patients with mCRC who were chemotherapy naïve but fit for first-line chemotherapy) and the internal validation by bootstrapping partly made up for this limitation.

Detection of deteriorated HRQoL overall or in specific areas should always be accompanied with defined intervention plans. Research on effective supportive strategies (nutrition, pain control, physical activity, etc.) was not included in the present pilot study. However, authors acknowledge that explorative analyses should always look at possible therapeutic implications. Future development of the present research will include also supportive care algorithms, in particular during anticancer therapy.

Conclusions

In conclusion, we were able to build a model which predicts the risk of having a deteriorated baseline quality of life in patients with mCRC, using basic anthropometric and lifestyle parameters.

Our results indicate that special attention ought to be paid to elderly, females or low weight patients. Increasing awareness of patients at risk of poor HRQoL will help in the direction of systematic and accurate implementation of quality of life assessment in daily practice and prioritization of supportive care strategies. Validation of the present nomogram in independent cohorts and in oncological settings other than mCRC is also underway.

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Footnote

Reporting Checklist: The authors have completed the MDAR

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2194). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Local Ethics and Scientific Committees (local Ethics Committee Approval ID: R.S. 102/17) and performed in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all individual participants included in the study.

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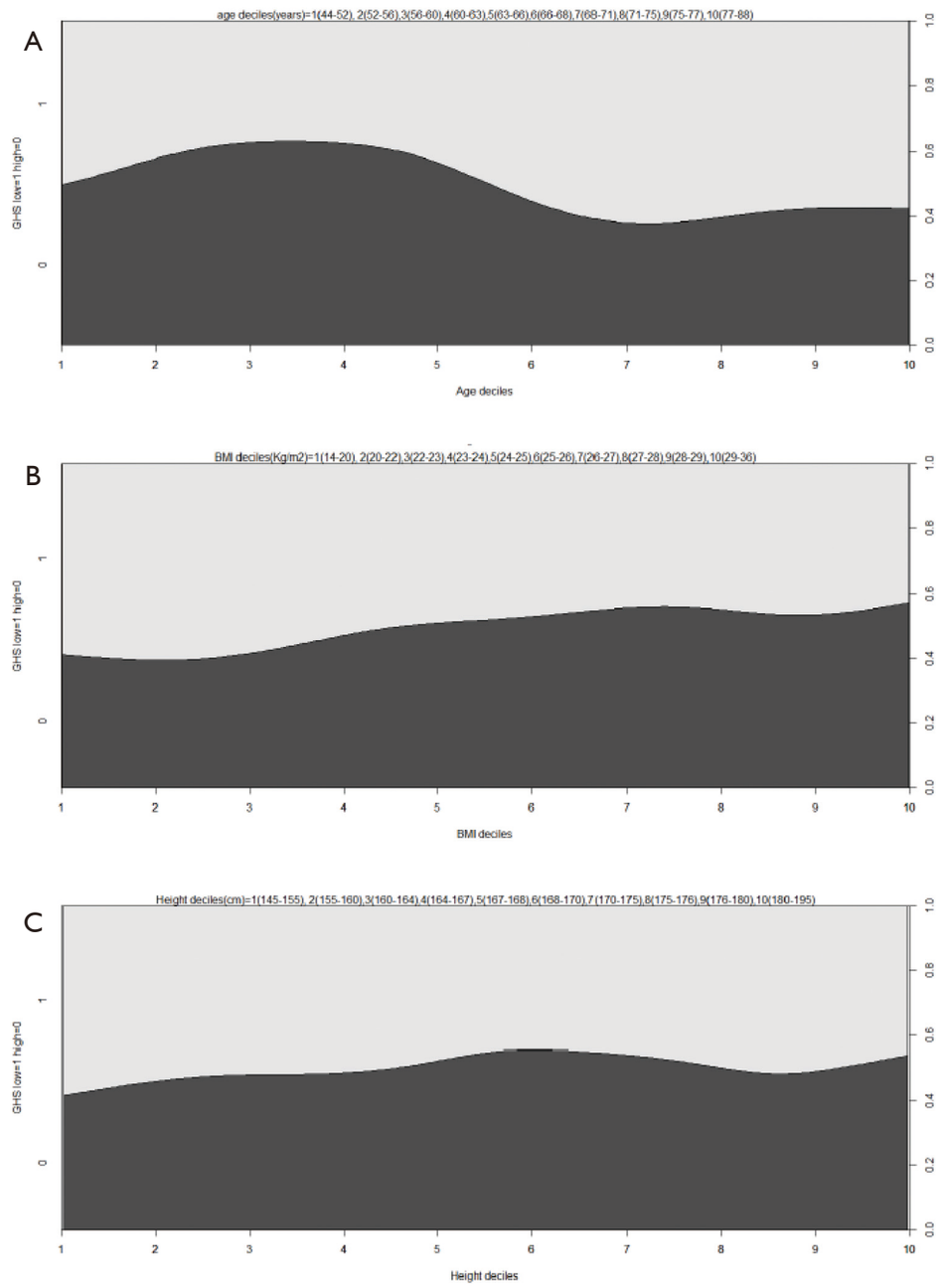

Figure S1 Smoothed frequency curves of low *vs.* high Global Health Score (GHS) for the continuous variables of age, height and BMI grouped by deciles.

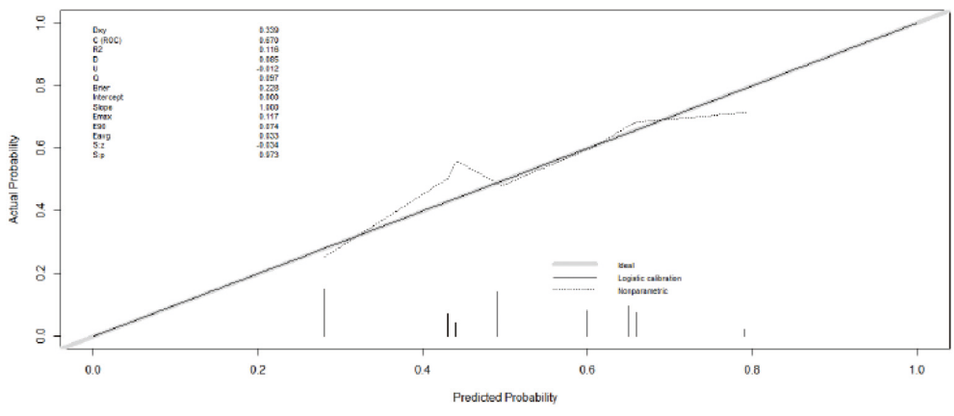

Figure S2 Apparent calibration of the model predicting Global Health Score (GHS) with three baseline variable (age, BMI and sex).

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