Objectively Measured Preoperative Physical Activity is Associated With Time to Functional Recovery after Hepato-Pancreato-Biliary Cancer Surgery: a Pilot Study

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Abstract
Surgical resection is currently the cornerstone of hepato-pancreato-biliary (HPB) cancer treatment. A low preoperative aerobic fitness level has been identified as a modifiable risk factor associated with complications after major abdominal surgery. A person’s aerobic fitness is influenced by performing moderate to vigorous physical activity (MVPA). This study aims to determine the activity monitor measured levels of MVPA performed among patients on the waiting list for HPB cancer surgery and their association with postoperative outcomes.

Methods:
A prospective, observational multi-center cohort pilot study was conducted. Patients enlisted for resection surgery on suspicion of HPB (pre)malignancy were enrolled. Performed MVPA was measured by an Actigraph wGT3X-BT. Additionally, aerobic fitness was measured via the Incremental Shuttle Walk Test, and (post)operative variables were collected from the electronic patient files. The association between MVPA and the pre and postoperative variables was determined by univariate and multivariate (logistic) robust regression.

Results:
A total of 38 participants, median age 66.0 (IQR 58.25 – 74.75) years, were enrolled. The median daily MVPA was 10.7 (IQR 6.9 – 18.0) minutes, only 8 participants met Dutch MVPA guidelines. Participants age, and incremental shuttle walk test score were associated with MVPA by multivariate statistical analysis. Time to functional recovery was 8 (IQR 5 - 12) days and was associated with MVPA and type of surgery (major/minor) in multivariate analysis.

Conclusion:
76% of patients enlisted for resection of HPB (pre)malignancy performed insufficient MVPA. A higher level of MVPA was associated with a shorter time to functional recovery.

Keywords:
Hepato-pancreato-biliary cancer, perioperative, preoperative, physical activity, time to functional recovery
Introduction

Hepato-Pancreato-Biliary (HPB) cancer is a frequently diagnosed disease with an incidence of 248,800 patients diagnosed with HPB cancer in Europe in 2018, of which pancreatic cancer constituted the majority with 132,600 diagnoses. (1) Since advancing age of the population is the most important factor contributing to the incidence of pancreatic cancer, the incidence and the average age of HPB cancer patients is set to increase in the coming years due to increasing life expectancy. (2,3) Surgical resection and adjuvant therapy are currently the cornerstone of treatment for HPB cancer. (4) Currently, approximately 20-30% of patients develop major postoperative complications which lead to increased length of hospital stay (LOS), decreased postoperative quality of life and delay to chemotherapy. (5–7) Since complications and mortality rates following pancreatic and liver surgery increase with advancing age, (8) identifying modifiable risk factors in HPB cancer patients may help to reduce postoperative complications, LOS and hospital costs. (9)

Preoperative aerobic fitness level has been identified as a modifiable risk factor in a variety of patients who need surgery. (10–12) A person’s aerobic fitness reflects the physiological reserve available to endure the physical stress of surgery and postoperative recovery. (13) Low preoperative aerobic fitness is associated with negative postoperative outcomes such as prolonged LOS and increase in incidence of unplanned readmissions, morbidity, and mortality after major intraabdominal surgery. (14,15) A person’s aerobic fitness is influenced by his or her physical activity (PA) level. (16,17) Consequently, current (inter)national guidelines for PA advocate to spend at least 150 minutes per week in activities with a moderate to vigorous intensity (MVPA). (18,19)

Multiple studies investigated the relation between preoperative (self) reported PA levels and outcome after surgery concluding that a higher preoperative level of PA is not significantly associated with the presence of postoperative complications (OR=2.60; 95%CI=0.59 to 11.37). However, it has been previously reported that PA is significantly associated with shorter LOS following abdominal surgery (OR=3.66; 95%CI=1.38 to 9.6). (20) Nevertheless, correlations between self reported PA and actual PA are generally low-to-moderate and ranging from R= -0.71 to 0.96. (21,22) Furthermore, previous studies have demonstrated that cancer patients overestimate their self-reported PA level when compared to objective measures. (23)
Therefore, insight into the level of actual, objectively measured, PA and subsequent postoperative outcomes in patients scheduled for HPB cancer surgery is needed in order to facilitate a patient’s postoperative recovery. The objective of this study was to determine activity monitor measured levels of MVPA and their association with postoperative outcomes as well as identifying associating modifiable factors among patients on the waiting list for HPB surgery.

Methods

Study design and study population

This prospective, observational multi-center cohort pilot study was performed at the University Medical Centre Groningen (UMCG), the Medical Center Leeuwarden (MCL), and the Medical Spectrum Twente (MST) in the Netherlands. All centers are connected via a Managed Clinical Network HPB surgery. Ethical approval was obtained from the Central Ethics Review Committee of the UMCG under registration number 201800539, and all participants provided written informed consent.

The research population consisted of adult patients scheduled for resection of HPB (pre)malignancy between October 2018 and September 2019. Exclusion criteria were 1) receiving an intervention aimed at influencing PA during the measurement period; or 2) receiving neo-adjuvant chemo(radio)therapy. Participants who wore the activity monitor for less than 6 days or did not undergo resection were excluded from analysis.

Data collection

Potential participants who met the inclusion criteria were identified by the responsible surgeon and were invited to participate immediately after being informed about their pending surgical procedure. After providing informed consent, baseline characteristics were collected consisting of age, length and weight, smoking behaviour- (yes/no), occupation (work/volunteer, yes/no), living- (alone/together), education- (lower/ higher), and alcohol consumption status. Alcohol consumption was coded as above the norm or equal to/ below norm of a maximum of one consumption per day as defined by the Dutch health council. (24) Lower education was defined as (preparatory) vocational or primary education and higher education as (preparatory) academic or higher education. Aerobic fitness was measured using
the Incremental Shuttle Walk Test (ISWT). The test was performed once, in accordance with
the Singh protocol. (25) The maximum walking distance expressed in meters and the
percentage of the predicted distance based on Probst et al., was used to determine a
participant’s aerobic fitness level. (26) Participants reaching a distance below 80% of the
predicted distance, were labelled unfit.

To determine the participants MVPA level, a hip worn activity monitor, the Actigraph
wGT3X- BT+ (Actigraph, Pensacola, FL, USA) was provided. (27–29) Instructions for use
included performing regular PA as they were used to and wearing the device for 7
consecutive days during waking hours. The used cut-off counts per activity intensity level
were sedentary time (<100 counts/min), moderate- (2020–5999 counts/min) and vigorous
intensity PA (≥5999 counts/min) with 100 Hz measurement epoch. (30) The total amount of
MVPA is determined both as the daily median of total accumulated minutes and as the daily
median minutes accumulated in at least 10-minute bouts, (19) where the latter is generally
defined as a 10-minute period with an interruption of no more than 2 minutes below the
threshold of 2020 counts per minute. (30) MVPA measured in 10-minute bouts was used for
further analyses. To identify non-wear time, the algorithm of Choi et al. (2011) was used. (31)
This algorithm defines non-wear times as periods of consecutive 0-counts for the duration of
90 minutes.

After completion of the measurement week, the symptom burden of the past 24 hours was
determined by completing a translated version of the “MD Anderson Symptom Inventory”
(MDASI) questionnaire. The MDASI median scores, and the sub-domain “symptom burden”
and “activity interference” scores were used to determine the participants symptom burden.
(32) Median scores are used per sub-domain. The activity monitor, and the MDASI were
returned to the researcher via mail. Lastly, (post) operative variables were collected from the
electronic patient files. These included the surgery type (target organ, major/minor surgery,
open/laparoscopic surgery). Major surgery was defined as any pancreatic, or liver resection of
at least three liver segments. (33) LOS was expressed in days between surgery and hospital
discharge as well as between surgery and functional recovery (FR). The latter was determined
by adequate pain control requiring oral analgesia only, no signs of active (wound)infection,
tolerance of solid foods and independent mobility sufficient to perform activities of daily
living at the preoperative level. (34) Mortality was defined as in-hospital mortality or within
30 days after discharge. Overall complications consisted of all surgical and non-surgical
complications within 30 days of surgery. Major complication was defined as any Clavien–Dindo grade ≥III complication. (35)

Statistical analyses

Statistical analyses were performed using R software version 3.6.1. (36) A p-value ≤ 0.05 was considered significant. Continuous data were summarized by median and interquartile range (IQR), categorical data by frequency and percentage. Range was reported if deemed relevant. All enlisted patients, recording 6 or more measurement days, were used in the MVPA analyses, participants only receiving an exploratory laparotomy or laparoscopy without resection and those who were eventually not operated upon were excluded from the complication’s analyses. Furthermore, participants that passed away within 30 days after discharge were excluded in the time to FR analysis. MVPA data are frequently non-normally distributed due to outlying observations for a few persons having PA levels away from the bulk of the data. A robust regression approach was undertaken throughout this study to prevent a large influence on the association coefficients by outlying observations. (37–39)

The association between the level of MVPA in 10-minute bouts and the preoperative variables, and time to FR and pre- and peri-operative variables was determined by univariate and multivariate robust regression. (40) Regardless of the small sample size, a multivariate robust regression approach was used to explore potential modifiable factors. Furthermore, uni- and multivariate robust logistic regression was used to determine the Odds Ratio (OR) of the occurrence of complications based on the preoperative and peri-operative variables. (38–40) All multivariate analyses were performed using the measured independent explanatory variables identified to potentially have a significant association with the dependent variable during univariate regression analysis. LOS analysis is reported in the supplementary material. Lastly, a subset analysis was performed to determine the association between MVPA in 10-minute bouts and time to FR within the major complications group via univariate robust regression.

Results

A total of 154 patients who met the inclusion criteria were approached for participation, 40 patients (26%) consented to participate in the study. Two participants were excluded from PA analysis due to not meeting wear-time criteria, the measurements from the remaining 38
participants were used for further analysis. Five participants had either no surgery procedure (one participant) or received a procedure without resection (exploratory laparotomy only, four participants). These patients were excluded from complications analyses. Furthermore, two participants were excluded from the time to FR analyses due to postoperative mortality. Figure 1 displays the flowchart of participant inclusion.

**Characteristics**

Of the 38 participants, 22 participants were male, and the mean age of participants in both the PA and surgery outcome group were 65.8 years (±9.4) and 65.5 years (±9.8), respectively. 22 participants were labelled unfit, with a median 69% (±31%) distance covered of the predicted ISWT distance in the PA group and 65% (±28%) in the surgery outcome group. Of the 33 participants that underwent the surgery procedure, 10 developed major complications. Participant characteristics and perioperative data are presented in Table 1.

**Physical activity**

The participants median level of MVPA was 10.7 minutes per day, wearing the activity monitor 66% (±29%) of waking hours per day. The MVPA variability between participants was large, ranging from zero to 60.1 minutes per day. Eight participants (21%) met the PA guideline of 150 minutes MVPA per week. The level of MVPA reduced with 0.52 minutes per advancing age year, ($R^2 = .31, p = .001$), and increased by .02 minutes per meter covered during the ISWT ($R^2 = .35, p = .008$), and subjects labeled as fit (7.90 minutes more in fit subjects, $R^2 = .20, p = .023$) were identified as correlating with MVPA via univariate robust regression. Since the aerobic fitness level was derived from the ISWT distance covered, this variable was omitted from multivariate regression. The multivariate regression model for performed MVPA determined by multivariate robust regression was $29.05 + \text{(ISWT (meters)} * 0.01) + \text{(Age (years) * -0.35)}$ (adj. $R^2 = .41$). The association between MVPA and preoperative variables via uni- and multivariate robust regression is displayed in Table 2.

**Complications**

Seventeen participants (51%) had complications of which ten (30%) were major. The association was found between MVPA and the presence of major complications ($OR = 0.99, 95\%CI= 0.95 – 1.04, p= .703$) was not statistically significant. A statistically significant association was found between the presence of major complications and BMI ($OR = .71,$
95%CI= 0.52 – 0.98, p=.036), % of predicted ISWT (OR= .98, 95%CI .97 – .99, p=.008) and surgery type (OR = .24, 95%CI = 0.06 – 0.95, p = .043). The odds of major complications decrease with increasing BMI, more distance covered on the ISWT compared to the predicated distance and a minor surgery procedure. The OR from multivariate robust logistic regression including surgery type and ISWT (% of predicted) was found to be: (surgery type (minor) * 0.144) + (ISWT (% of predicted) * 0.948). The OR from robust univariate and multivariate logistic regression for the occurrence of major complications are displayed in Table 3.

Time to functional recovery
The median time to FR was 8 (IQR 5 - 12) days, ranging from 2 till 56 days. Higher MVPA in both total accumulated bouts (-0.07 less days per minute increase, p=.009), and 10-minute bouts (-0.14 less days per minute increase, p=.007), a minor surgery procedure (-6.39 less days, p=.001), and a higher BMI (-0.46 less days per kg/cm² increase, p=.006) resulted in less time to FR. The multivariate model yields an adj. R²=.43, the model is as follows 12.54 + (MVPA (minutes) * -.08) + (surgery size (1 if minor, 0 if major) * -5.64). The association between MVPA in 10-minute bouts and time to FR in the subset where major complications occurred was -0.352 less days to FR per minute increase (R²=.460, p=.023). Time to FR analysis is displayed in Table 4.

Discussion
To our knowledge, this is the first study investigating activity monitor measured MVPA levels in HPB resection candidates not receiving PA interventions. Patients scheduled for HPB surgery engage in low daily MVPA whilst waiting. Furthermore, a relation was found between the level of MVPA and time to FR after HPB surgery for (pre)malignancy; patients with higher levels of PA require less time to FR. The current findings suggest that increasing a patient's pre-operative MVPA level would improve the postsurgical outcome.

Physical activity
The median MVPA level measured in the current study was low but comparable to other preoperative activity monitor measured MVPA studies, e.g. gastric bypass and lumbar fusion surgery. (41,42) However, this comparison is somewhat arbitrary due to the influence of age, and the variety in symptom burden experienced amongst different pathologies. Furthermore, the variety in activity monitor device configuration like MVPA cut-off point and wear-time validation highly influences the results. (43) Nevertheless, this study demonstrates that the
majority (79%) of the patients, enlisted for HPB surgery did not perform sufficient MVPA to meet the guideline of 150 minutes MVPA per week. (18,19)

These findings might be explained by the psychological impact of being enlisted for surgery because of malignancy. Namely, being informed about the presence of a tumor can result in changes in PA behavior. (44) Participants were recruited directly after being enlisted and measurements were performed during the first week after enlistment. Due to the design of the study, it remains unclear whether this effect is temporarily, the performed minutes of MVPA might reach higher levels over time. Previous studies have reported an increase in PA during the waiting period. (45) The observed increase might have been caused by an increased awareness or social desirability of the participant, as they had to fill in physical activity questionnaires or had to perform physical fitness measures during this study. Furthermore, it seems likely that patients perform less MVPA due to the interference of tumor related symptoms. However, there was no evidence for an association between the experienced symptom burden like pain and fatigue, measured with the MDASI, and the level of performed MVPA. Notably, participants experienced fairly low symptom interference in our study, 1.87 points on mean out of 10. It therefore seems probable that subjects with high symptom interference were more likely to reject study participation. Due to the small sample size, no subcategory analysis with subjects experiencing high levels of symptom burden could be performed.

**Post-operative outcomes**

A significant association was found between MVPA and time to FR (R²= 0.17, p=.006) but no significant association was found between MVPA and the occurrence of postoperative complications (OR = 0.99, 95%CI= 0.95 – 1.03, p= .67). These findings are in accordance with the systematic review and meta-analysis in preoperative cancer patients by Steffens et al., who found an association between higher levels of preoperative MVPA and a shorter absolute LOS (OR=3.66; 95%CI= 1.38 to 9.6), but not with postoperative complications (OR=2.60; 95%CI=0.59 to 11.37). The majority of studies in this meta-analysis used self-reported MVPA and participants undergoing neo-adjuvant (physical)therapy. (20) However, the meta-analysis as well as the current study consistently indicate that higher levels of MVPA positively influences a patient’s capacity to endure the demands of surgery. (20)
A subject’s level of preoperative MVPA was associated with reduced time to FR, 43% of the time to FR could be explained via multivariate robust regression including surgery size and MVPA levels. This reduction might be explained by the lower relative capacity needed to perform activities in daily living by patients with higher levels of aerobic fitness. FR is determined by both functional and physiological criteria, higher levels of aerobic fitness increase a patient’s functional capacity to perform activities of daily living. (46) Therefore, patients performing more MVPA during the preoperative phase have higher levels of aerobic reserve to perform activities of daily living. These reserves might contribute to the recovery during the post-operative phase.

Furthermore, a higher level of aerobic fitness was associated with reduced OR for the occurrence of major postoperative complications found by univariate robust regression. Similar reductions have been reported in multiple studies amongst a large variety of surgical procedures. (7,10–13) These reductions might be explained by the higher aerobic reserves enhancing the bodies capacity to cope with the responses to the surgical procedure. Nevertheless, aerobic fitness was not found to have a significant association in multivariate robust regression including surgery size. Notably, the current study found lower OR for the occurrence of major complications in subjects with a higher BMI. This result is inconsistent to previous studies showing increased OR for the development of major complications in obese and overweight subjects undergoing pancreatectomy procedures. (47) This difference might be explained by the overrepresentation of subjects with high BMI scores undergoing a major surgery procedure in the present study. (Wilcoxon rank sum test, W = 74, p= .02)

Major surgery has a higher risk of resulting in major complications. Therefore, BMI was removed from multivariate regression analysis in the current study. Additionally, we found a reduction in time to FR after major complications in subjects performing higher levels of PA. Therefore, it could be concluded that because subjects with a higher level of MVPA have more capacity to cope with the demands endured by complications, the impact of complications is less. Nevertheless, these results should be interpreted with some caution since only nine subjects reached FR after major complications.

Treatment opportunity
This study identifies preoperative MVPA as a modifiable patient factor to reduce time to FR. Multiple associations between performed MVPA and preoperative variables were found, namely MVPA decreased with advancing age with 0.52 minutes per age year (p=<.001), and increased in participants with higher aerobic fitness, covering more distance during the ISWT
(0.02 minutes per meter, p=.008). Since both PA and aerobic fitness declines with age, these findings underpin the hypothesis that unfit and older patients could benefit most from interventions aimed to improve aerobic fitness and to increase MVPA levels, especially in the waiting time before surgery. Furthermore, although this study does not include a detailed cost analysis, increasing the level of preoperative MVPA via relative low-cost treatment modalities as education, wearables and physiotherapy, may be of particular relevance for the reduction of hospital costs due to the shorter hospital stay (see supplementary data). (9)

Limitations
There are some limitations to this observational study. The first is that the study did not reach full accrual, which limits the power and may have had an impact on results with a higher risk of type II errors. Since a limited number of HPB resections are yearly performed, participants were included via convenience sampling in a multi-center design. However, the final sample size obtained is comparable with other studies aimed at measuring PA via activity monitor devices in major abdominal surgery. (49,50) Nonetheless, only 26% of the approached subjects provided consent to participate in the study. A reason for this low participation rate might have been the moment of inclusion, namely directly after being enlisted for surgery. Frequently mentioned reasons for declining participation were the feeling of being emotionally overwhelmed and currently not having the energy to endorse participation. These reasons might have induced a sample slightly biased in the direction of somewhat fitter patients. Larger sample sizes and less strenuous PA measurements can be more easily acquired via questionnaires. Nevertheless, activity monitor measured PA is a feasible and more reliable method of determining PA and therefore recommended. (20,41)

Conclusion
This study demonstrates that 79% of the patients, enlisted for resection of HPB (pre) malignancy performed insufficient MVPA. A higher level of MVPA, objectively measured with an activity monitor was independently associated with a shorter time to FR. However, levels of MVPA were not associated with postoperative complications. Stimulating MVPA in the waiting time for surgery might help to reduce the LOS. These findings add to a growing body of evidence suggesting that higher levels of MVPA positively influence a patient’s capacity to endure the demands of surgery and improve the outcome of surgery.
Abbreviations
MVPA – Moderate to vigorous physical activity
PA – Physical activity
HPB – Hepato-pancreato-biliary
LOS – Length of hospital stay
FR – Functional recovery
ISWT – Incremental Shuttle Walk Test
MDASI – MD Anderson Symptom Inventory
BMI – Body mass index
OR – Odds ratio
IQR – Interquartile range

Ethical approval and consent to participate
Ethical approval was obtained from the Central Ethics Review Committee of the UMCG under registration number 201800539, and all participants provided written informed consent.

Consent for publication
Not applicable.

Availability of data
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest
The authors declare that they have no competing interests.

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Authors’ contributions
CM was first author of the manuscript, performed data collection and analysis. WK aided in the draft of the manuscript and statistical analysis. TT, CS and JK aided the writing of the manuscript. HE and DL aided the data collection process. All authors critically reviewed the article. The authors read and approved the final manuscript.
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