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# Recovery of Lung Function, Dominant Handgrip Strength, and Health-Related Quality of Life in Cardiac Surgical Patients Following Hospital Discharge

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### **Abstract**

Purpose: Assessment of recovery in post-cardiac surgical patients is commonly conducted using lung function, dominant handgrip strength (DHGS), and health-related quality of life (HRQoL). The aim of this study was to determine the recovery of lung function, DHGS and HRQoL in cardiac surgical patients at sixweeks and six-months after hospital discharge. Further, this study investigated the association between these parameters and the predictive ability of DHGS for lung function and HRQoL. Methods: This was a prospective observational study that involved 58 cardiac surgical patients who completed lung function, DHGS, and HRQoL assessments pre-operatively, at six-weeks, and six-months after hospital discharge. Lung function was assessed using three different calibrated spirometers, while DHGS was measured using three different calibrated handgrip dynamometers. The Short-Form 36 questionnaire was utilized for HRQoL assessment. Results: At six-weeks after hospital discharge, lung function and DHGS were significantly (pConclusion:Variable changes were identified in lung function, DHGS, and HRQoL in cardiac surgical patients at six-weeks and six-months after hospital discharge. Dominant hand grip strength may have limited or no value in predicting lung function and HRQoL in cardiac surgical patients during the intermediate recovery period.

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### **ABSTRACT**

**Purpose:** Assessment of recovery in post-cardiac surgical patients is commonly conducted using lung function, dominant handgrip strength (DHGS), and health-related quality of life (HRQoL). The aim of this study was to determine the recovery of lung function, DHGS and HRQoL in cardiac surgical patients at six-weeks and six-months after hospital discharge. Further, this study investigated the association between these parameters and the predictive ability of DHGS for lung function and HRQoL. **Methods:** This was a prospective observational study that involved 58 cardiac surgical patients who completed lung function, DHGS, and HRQoL assessments pre-operatively, at six-weeks, and six-months after hospital discharge. Lung function was assessed using three different calibrated spirometers, while DHGS was measured using three different calibrated handgrip dynamometers. The Short-Form 36 questionnaire was utilized for HRQoL assessment. **Results:** At six-weeks after hospital discharge, lung function and DHGS were significantly (p<0.001) reduced, while only lung function improved to preoperative levels by six-months. Pre-operative and six-week assessments revealed similar HRQoL, which continued to improve by six-months. At six-weeks and six-months after hospital discharge, there were significant (p<0.001) and moderate associations between DHGS and lung function, but DHGS was not a significant predictor of lung function. There were no associations between DHGS and HRQoL. **Conclusion:** Variable changes were identified in lung function, DHGS, and HRQoL in cardiac surgical patients at six-weeks and six-months after hospital discharge. Dominant hand grip strength may have limited or no value in predicting lung function and HRQoL in cardiac surgical patients during the intermediate recovery period.

**Keywords:** muscular strength, respiratory function test, quality of life, cardiovascular diseases, cardiac surgery.

### **INTRODUCTION**

Recovery after cardiac surgery is a multi-dimensional process that involves the resolution of adverse symptoms and restoration of functional capacity to either pre-surgical or greater levels. <sup>1</sup> Successful recovery is achieved through the use of advanced surgical techniques and early cardiac rehabilitation programs that aim to avoid hospital re-admission, prevent post-operative pulmonary complications, and ensure patient's re-integration into routine activities of daily living. <sup>2</sup> Within clinical settings, monitoring of patients' recovery after cardiac surgery is routinely conducted using lung function, dominant handgrip strength (DHGS) and health-related quality of life (HRQoL) tools. 3-5 These tools are utilized to monitor patient progression as well as identify patients at higher risk of post-operative complications.<sup>3,6</sup>

To date, several studies have examined the recovery of lung function, DHGS, or HRQoL in cardiac surgical patients at various timepoints. These studies have focused primarily on the acute (i.e. in-hospital and prior to discharge) and long term (i.e. after six-months) recovery phases.<sup>3-5,7-10,11-14</sup> Examination of intermediate patient recovery within six-months of hospital discharge has been limited with contradictory findings reported for the recovery of lung function, DHGS, or HRQoL.4.7,15,16 For instance, Sahu et al reported that lung function had returned to pre-operative levels at six-months after cardiac surgery, while Rouhi-Boroujeni et al reported that most lung function indices had not recovered at six-months post-operatively.15,17 When compared to pre-operative values, DiMaria-Ghalili et al reported similar DHGS at four to six-weeks post-operatively, whilst da Silva et al reported a significant increase in DHGS at three-months post-operation.<sup>7,18</sup> Similarly, Gunn et al reported poorer HRQoL for patients at six-months after hospital discharge while Gjeilo et al identified improved HRQoL at six-months following cardiac surgery.<sup>12,19</sup> These discrepancies highlight a limited understanding of the recovery trajectories of lung function, DHGS, and HRQoL and the need for more work to support clinicians in planning future therapies.<sup>20</sup>

During the intermediate recovery phase, assessment of lung function may be performed in smaller clinics in rural/regional areas that may have restricted availability to spirometers and/or inadequate spirometry training.<sup>21</sup> Therefore, the use of tools that indirectly assess lung function may be important to clinicians and provide greater medical care in these smaller clinics. Previously, DHGS was reported to be significantly associated with lung function in patients undergoing cardiac surgery and a predictor of lung function before cardiac surgery. To our knowledge, no study has assessed the predictive ability of DHGS in post-cardiac surgical patients with a prior study reporting DHGS as a timely indicator of HRQoL in cancer survivors.<sup>22</sup> Therefore, the aims of this study were to determine the intermediate recovery period of the: 1) changes in lung function, DHGS, and HRQoL in cardiac surgical patients at six-weeks and six-months after hospital discharge; 2) association between lung function, DHGS, and HRQoL; and 3) predictive ability of DHGS for lung function and HRQoL. Confirmation of associations and predictive ability of DHGS for lung function during the intermediate recovery period would provide clinicians with a simple tool to easily monitor patient progress and therapy success.

### **METHODS**

### **Study Design and Participants**

This study employed a prospective, observational design and was carried-out between June 2020 and September 2021 in two regional hospitals in North Queensland. Dominant HGS, lung function, and HRQoL of participants were assessed by qualified health practitioners a day before cardiac surgery and at six-weeks and six-months after hospital discharge. The study was approved by the Human Research Ethics Committee, Townville University Hospital (HREC/2019/QTHS/53274) and written informed consent was obtained from each participant before participation. The study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN1261900151XXX).

Participants were adults (aged ≥18 years) who had the ability to speak, read, and comprehend English and were scheduled to undergo elective cardiac surgery at the involved hospitals. The cardiac surgical procedures experienced by participants included coronary artery by-pass graft (CABG), valvular replacements/repairs, or a combination of both. Participants were excluded from the study if they had an existing neuromuscular condition, upper limb deformities, carpal tunnel syndrome, neurocognitive or mental health disorders, had undergone hand surgery in the last three months, or were pregnant.

### **Data Collection Procedures**

Demographic data obtained from the participants' medical records included age, sex, height, weight, body mass index, ethnicity, smoking and alcohol consumption status, highest education attained, employment status, and self-reported physical activity level. Clinical characteristics noted were pre-existing comorbidities, type of scheduled cardiac surgery, New York Heart Association (NYHA) classification, aortic cross clamp time in minutes, cardiopulmonary bypass time in minutes (CPBT), left ventricular ejection fraction (LVEF), and the Acute Physiology and Chronic Health Evaluation III score. During the follow-up assessments, participants rated their pain during coughing using a numerical scale  $(0 =$  no pain to  $10 =$  worst pain ever), as this may last up to four-months after cardiac surgery and impact upon lung function.<sup>9</sup>

### **Measurements**

### *Lung Function*

Pre-operatively, participants' lung function was measured using a calibrated spirometer (i.e., Vitalograph Alpha 6000, Vitalograph Ltd, Ireland; EasyOne Model 2001, NDD Medical Technologies, Switzerland) that was available at each hospital. Similarly, follow-up assessments were conducted using a calibrated spirometer (i.e., Vitalograph Alpha 6000; Microlab CareFusion, Yorba Linda, CA; CONTEC-SP10 Model, CONTEC Medical systems Ltd, China) that was available at the individual follow-up sites within a regional setting. Lung function assessments were conducted with participants in a sitting position and followed the guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS).<sup>23</sup> In line with the repeatability and acceptability criteria of the ATS/ERS, a minimum of three trials were conducted to measure the forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC), and the peak expiratory flow rate (PEFR), with the highest values utilised for statistical analyses.<sup>23</sup> Further, predicted FEV<sub>1</sub> and FVC, based upon participant's age, sex, height and ethnicity, were calculated using the prediction models proposed by the global lung initiative [\(http://gli](http://gli-calculator.ersnet.org/index.html)[calculator.ersnet.org/index.html\)](http://gli-calculator.ersnet.org/index.html). These values were expressed as a percentage (%) and were considered normal if ≥80%. 10 Changes in FEV1, FVC, and PEFR at six-weeks ([six-weeks – pre-operative]/pre-operative x 100) and six-months ([six months – pre-operative]/pre-operative x 100) were also calculated and utilised for analysis. Since various brands of spirometers were utilised across the region, and typical for normal clinical practice, all spirometry results were normalised to a reference device (Vitalograph Alpha 6000) via unique regression equations for analyses.

### *Dominant Handgrip Strength*

Pre-operatively, participants' DHGS was measured using a calibrated Jamar hydraulic dynamometer (i.e., Model 5030J1, Patterson Medical, Warrenville, IL; Model 5030J1, Performance Health, China) at each hospital. Follow-up assessments were conducted using a similar and calibrated hand dynamometer (i.e., Model 5030J1, Performance Health; Model J00105, Sammons Preston, Bolingbrook, IL; Model EH101, Zhongshan Camry Electronic Co., Ltd, China) at the individual follow-up sites. All DHGS assessments were conducted in accordance with the guidelines of the American Society of Hand Therapists (ASHT). All Jamar dynamometers were set at the second handle position while the Camry dynamometer was adjusted to the third position to correspond to the two-centimetre difference between the moveable and stationary handles of the Jamar dynamometers. During the assessment, participants sat in a chair without an armrest with the elbow in 90° flexion, shoulder fully adducted, while the forearm and wrist were placed in neutral position. <sup>24</sup> Standardised instructions as per the ASHT recommendations were given to the participants who were required to complete a minimum of three trials with the greatest value accepted as the DHGS result.<sup>24</sup> As various hand dynamometer brands were utilised across these regions, and typical for normal clinical practice, all DHGS results were normalised to a reference device (Jamar hydraulic dynamometer, Model 5030J1, Performance Health) via unique regression equations for analyses.

### *Health-Related Quality of Life*

The Short Form-36 medical outcome version 2 (SF-36V2) questionnaire was used to assess patient-reported HRQoL. This multi-faceted instrument was composed of 36 items, which primarily assessed the physical and mental components of HRQoL using scoring algorithms and normalised for Australians.<sup>25</sup> The SF-36V2 scoring ranged from 0 to 100 with values greater than 50 indicating good HRQoL while values less than 50 indicating poor HRQoL.<sup>26</sup>

### **Statistical Analyses**

A minimum of 53 participants (80% power, p<0.05) was needed to identify a significant change in DHGS based on prior work and an effect size of 0.55. Normality of distribution was verified using the Kolmogorov-Smirnov test and Lilliefors correction, with the application of the central limit theorem allowing the use of parametric statistical analyses.<sup>27</sup> Recovery of lung function, DHGS, and HRQoL at six-weeks and six-months were analysed using the repeated measures analysis of variance with Bonferroni correction applied for post-hoc multiple comparisons. Pearson correlation coefficients categorised either weak (0- 0.30), moderate (0.31-0.70) or strong (0.71-1.0) associations between lung function, DHGS and HRQoL. Multiple regression analysis was used to determine the ability of DHGS to predict lung function and HRQoL values. Data was presented as frequency or mean (standard deviation) and the level of significance was set at <0.05. Pearson Chi square was used to compare participants lost to follow-up and those who completed all assessments at six-months, while simple regression models were used to conduct sensitivity analyses for missing data. All statistical tests were conducted using the IBM SPSS Statistics 27 (IBM Inc, Chicago IL).

### **RESULTS**

### **Participants' Characteristics**

Out of 120 participants initially recruited for this study, only 58 participants completed DHGS, lung function, and HRQoL assessments at all time-points. Reasons for attrition are shown in Fig. 1. Differences between the participants who were lost to follow-up and those who completed all assessments were only identified for ethnicity, discharge destination, and ischaemic heart disease, which had minimal to no impact on DHGS, lung function, and HRQoL (results not shown). At baseline, lower estimates were observed for the 58 participants who completed all assessments compared to the original 120 participants, although no significant difference was identified between the relative efficiencies of these two groups (results not shown).



**Figure 1.** Flow diagram of the study participants.

Participants were mostly aged over 65 years, non-indigenous males (82%) who completed high school education and presented with pre-existing comorbidities such as hypertension and dyslipidaemia (Table 1). None of the participants reported having sternotomy-related pain during coughing at the time of follow-up assessments. Other participants' demographic and clinical characteristics are shown in Table 1.

**Table 1**. Demographic and clinical characteristics (n =58 unless otherwise stated).

Variables	
Sex (males) <sup>t</sup>	48(82%)
Age (years) <sup>#</sup>	67.0(9.3)
Height (m) <sup>#</sup>	1.71(0.09)
Weight (kg) <sup>‡</sup>	89.4(19.1)
Body Mass Index (kg/m <sup>2</sup> ) <sup>‡</sup>	30.37 (5.68)
Ethnicity <sup>†</sup>	
Indigenous	3
Non-indigenous	50
Others	5
Smoking status <sup>t</sup>	
Never smoked	25
Ex-smoker	30
Current smoker	3
Highest educational level <sup>t</sup>	
Primary	1
High school	45
Tertiary	12
Physical activity level <sup>t</sup>	
Active	57
Inactive	1
Employment status <sup>t</sup>	
Employed	19
Unemployed	$\overline{4}$
Retired	35
Hand Dominance <sup>t</sup>	
Right	49
Left	8
Ambidextrous	1
Type of operation <sup>†</sup>	
<b>Isolated CABG</b>	43
<b>Isolated AVR</b>	$\bf 8$
<b>Isolated MVR</b>	3
CABG+AVR or MVR	4
<b>NYHA<sup>t</sup></b>	
	23
$\label{eq:1} \prod_{i=1}^n \left\{ \prod_{i=1}^n \frac{1}{n_i} \right\}$	18
$\begin{array}{c} \hline \end{array}$	17
IV	0
Left ventricular ejection fraction ( $n = 54$ ) <sup>‡</sup>	56.3(12.4)
APACHE score ( $n = 32$ ) <sup>‡</sup>	48.2(13.3)
CPBT in minutes ( $n = 55$ ) <sup>‡</sup>	112.3(41.6)
Aortic cross clamp time in minutes ( $n = 55$ ) <sup>‡</sup>	82(30)
Comorbidities <sup>t</sup>	
COPD	4
GORD	14
Obesity	24
T <sub>2</sub> DM	25
Dyslipidaemia	35
Hypertension	44

APACHE III - Acute physiology and chronic health evaluation III; AVR – Aortic valve replacement; CABG – Coronary artery by-pass graft; COPD – Chronic obstructive pulmonary disease; CPBT – Cardiopulmonary bypass time; GORD – Gastro-oesophageal reflux disease; MVR – Mitral valve replacement; NYHA – New York heart Association; T2DM – Type 2 diabetes mellitus. †Data presented as frequency (%)

‡Data presented as mean (standard deviation)

### **Recovery of Lung Function, Handgrip Strength, and Health-Related Quality of Life**

Pre-operatively, predicted FEV<sub>1</sub> [83.6(15.6) %] and FVC [83.2(15.0) %] indicated that participants had normal lung function patterns. At six-weeks after hospital discharge, significantly (p<0.05) lower FEV<sub>1</sub> (~13%), FVC (~8%), PEFR (~7%) and DHGS  $(-10%)$  were identified when compared to their pre-operative values. At six-months after discharge, FEV<sub>1</sub>, FVC and PEFR values had improved and were similar to their pre-operative values (Table 2). Conversely, DHGS remained lower at six-months (3%) after discharge compared to the pre-operative value. For HRQoL, the physical and mental components were similar between the pre-operative and six-week timepoints but had increased (10-26%) at six-months following hospital discharge (Table 2).

**Table 2**. Pre-operative and recovery values of lung function, dominant handgrip strength and health-related quality of life.



Values are mean (SD); FEV<sup>1</sup> – Forced expiratory volume in one second; FVC – Forced vital capacity; PEFR – Peak expiratory flow rate; DHGS – Dominant handgrip strength; PCS – Physical component score; MCS – Mental component score.

 $* = p < 0.05$  vs Pre-operative;  $** = p < 0.05$  vs. six-weeks.

### **Association between Lung Function, Handgrip Strength and Health-Related Quality of Life**

Significant moderate associations (0.41-0.67) were identified between DHGS and lung function pre-operatively, at six-weeks and six-months after hospital discharge (Table 3). These associations were strongest prior to surgery and weakest at sixweeks following hospital discharge. Conversely, there were no significant associations between DHGS and HRQoL at any timepoint (Table 3).

**Table 3**. Association between dominant handgrip strength, lung function and health-related quality of life prior to (Pre), and six-weeks and six-months following cardiac surgery.



CI – Confidence interval; FEV<sub>1</sub> – Forced expiratory volume in one second; FVC – Forced vital capacity; PEFR – Peak expiratory flow rate; DHGS – Dominant handgrip strength; PCS – Physical component score; MCS – Mental component score; Pre – Pre-operative; r-value – Pearson correlation coefficient; p-value – significance level.

### **Predictive Ability of Dominant Handgrip Strength for Lung Function and Health-Related Quality of Life**

At six-weeks and six-months post discharge, regression analysis showed that DHGS measured at each timepoint was not a significant predictor for lung function or HRQoL. However, pre-operative values of lung function, dyslipidaemia and sex of

the participants were identified as significant predictors and accounted for 52-63% and 55-73% of the variabilities in lung function at six-weeks and six-months, respectively (Table 4). For the physical and mental components of HRQoL, only their respective pre-operative values were identified to be significant predictors at six-weeks and six-months after hospital discharge (Table 4).



B – Unstandardised coefficient; CI – Confidence interval; FEV<sub>1</sub> – Forced expiratory volume in one second; FVC – Forced vital capacity; MCS – Mental component score; PCS – Physical component score; PEFR – Peak expiratory flow rate; pvalue – significance level;  $SB_E$  – Standard error of the coefficient. Pre-op – pre-operative.

### **DISCUSSION**

This study demonstrated that lung function and DHGS were significantly reduced at six-weeks post discharge with only lung function improving to pre-operative levels by six-months. In contrast, the physical and mental components of HRQoL were similar between pre-operative and six-week assessments and continued to improve up to six-months after discharge. Although moderate associations between lung function and DHGS were identified at six-weeks and six-months, DHGS was not a significant predictor of lung function at these times. Overall, this study demonstrated that lung function, and not DHGS, had recovered by six-months following hospital discharge with HRQoL improved for post-cardiac surgical patients. Further, a simple assessment like DHGS failed to predict lung function and HRQoL during the intermediate surgical recovery period, with this tool of limited use for clinicians to indirectly assess these parameters.

As expected, lung function and DHGS were lower for patients at six-weeks after hospital discharge, likely due to deconditioning associated with the surgery and the restrictive sternal precautions given to these patients at the time of discharge.<sup>28</sup> These activity restrictions include limited range of motion and/or load applied to the upper limbs and trunk that typically last six-weeks or longer and possibly lead to weaker forearm/hand muscles assessed via DHGS. <sup>29</sup> These constraints along with sternal healing likely led to sub-optimal involvement of the respiratory muscles and hence reduced lung function observed in the current study. 28,30 Most participants reported that they only commenced their phase II cardiac rehabilitation program at the fifth week after surgery, which may have contributed additionally to the sub-optimal recovery of respiratory and musculoskeletal

function in the initial six-weeks.<sup>31</sup> Further, most patients were likely performing only activities of daily living (e.g. walking, showering) with minimal or no difficulty within the initial six-weeks, which resulted in self-reported, below-average physical function (PCS). Thereafter, DHGS and PCS improved with an accompanying increase in lung function, likely as a result of increases in regular physical activity and/or independent mobility.<sup>32</sup> Similarly, MCS was improved beyond the initial six-weeks with patients adjusting to the reduced burden of cardiac disease and/or surgery.<sup>33</sup>

A key finding of the current study was that lung function had recovered to pre-operative values by six-months after hospital discharge. This finding contradicted a previous study, which found a significant decrease in lung function indices (FEV<sub>1</sub> and PEFR) at six-months after cardiac surgery.<sup>15</sup> Participants in the current study demonstrated a higher pre-operative functional status, as indicated by a higher proportion of patients (70%) categorised within NYHA class I-II that may possibly explain the quicker recovery of lung function. Other possible contributors to the lung function recovery could include the easing of the sternal precautions, which might have allowed participants to undertake more intense physical activities and increased lung expansion and greater lung volumes. <sup>32</sup> Improvement in HRQoL from six-weeks to six-months after discharge may further support the potential involvement of patients in more physical activities with similar and significant improvements in physical and mental components of HRQoL observed in prior studies. 12,14

Whilst the PCS continued to improve at six-months after hospital discharge, the DHGS still remained below pre-operative values for the current patients, indicating that the PCS and DHGS assess different domains of physical function. <sup>34</sup> The predominance of retired, older male participants, who were likely to not engage in upper limb strengthening exercises, in the current study may explain the delayed recovery of DHGS.<sup>35</sup> Previously, da Silva et al identified full DHGS recovery at threemonths post-operatively, however, most of their participants were deconditioned (median DHGS of 14.8 kgf) with a quicker recovery reported due to lower initial levels.<sup>7</sup> Further studies examining the recovery trajectory of DHGS in cardiac surgical patients may consider involving longer follow-up (e.g. one year) to enhance understanding of the recovery processes in this population.

Another notable observation was the significant but moderate associations between lung function and DHGS. Similar associations were reported for unhealthy populations (e.g., chronic obstructive pulmonary disease, diabetes, stroke) that reflect a potential physiological link between peripheral and respiratory skeletal muscles. 36,37 Despite this potential link, DHGS was not identified as a significant predictor of lung function at six-weeks and six-months in the current study. Further, DHGS was not predictive of lung function at hospital discharge in cardiac surgical patients. Collectively these findings suggest that any link between DHGS and lung function may be indirect at best, and possibly via a mediator such as physical activity intensity or fitness level.<sup>38</sup> Future studies may clarify the role of physical activity intensity or fitness level in moderating the recovery of the musculoskeletal and respiratory systems in post-cardiac surgical patients.

While DHGS was not predictive of lung function and HRQoL, the current study identified pre-operative lung function and HRQoL results as significant predictors for six-week and six-month lung function and HRQoL, respectively. These findings support prior work with pre-operative assessments being important prognostic tools for the recovery of patients undergoing cardiac surgery.<sup>39,40</sup> In contrast, DHGS may have limited, if any, clinical value in indirectly estimating the intermediate recovery of lung function and HRQoL for future therapy of post-cardiac surgical patients.

#### **Limitations**

To our knowledge, the present study was the first longitudinal study that examined the prediction of lung function and HRQoL using DHGS at six-weeks and six-months after hospital discharge in cardiac surgical patients. Further, the current study engaged with a range of regional clinics and standardised the use of different types of dynamometers and spirometers typically used in clinical practice. Despite these strengths, there were some limitations that future studies may want to consider. This study had a significant dropout rate (52%), which was not unusual for research in regional areas, especially given the COVID-19 pandemic that prevailed during the data collection phase of the study.<sup>7</sup> The sample size was, nevertheless, adequately powered to detect changes in DHGS and to determine its predictive potential in these participants. Future studies may examine a larger sample size in order to confirm and expand upon our findings. Another limitation was that involving a high proportion of patients undergoing CABG (71%) may have skewed the findings and limited the generalisability of the results to patients undergoing valvular replacements/repairs. Given the differences in lung function recovery between CABG and valvular surgeries [10], future studies may consider examination of the impact of type of surgery on the recovery of DHGS, lung function and HROoL.

### **CONCLUSION**

In cardiac surgical patients, improvements in HRQoL and lung function recovery occurred within six-months following hospital discharge. In contrast, DHGS had not recovered to pre-operative levels by six-months and notably was not identified as a predictor of lung function or HRQoL. Therefore, DHGS may have limited or no use as an indirect prognostic marker of lung function and HRQoL in cardiac surgical patients within six-months after hospital discharge.

### **Declaration of interests:** All authors have no conflict of interest to declare.

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