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# Body composition and pelvic fat distribution are associated with prostate cancer aggressiveness and can predict biochemical recurrence

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**Abstract**

This study evaluated the effect of body composition and pelvic fat distribution on the aggressiveness and prognosis of localized prostate cancer. This study included patients who underwent robot-assisted radical prostatectomy with positive surgical margins. Clinicodemographic data were collected from patients' medical reports. Pretreatment magnetic resonance images (MRI) obtained for cancer staging were reviewed by a single radiologist to calculate pelvic fat distribution and body composition. We correlated these body composition parameters with initial prostate-specific antigen (iPSA), Gleason score, extracapsular tumor extension, and biochemical recurrence (BCR)–free survival. The iPSA was significantly associated with body mass index (BMI; $P = .027$), pelvic fat volume ($P = .004$), and perirectal fat volume ($P = .001$), whereas the Gleason score was significantly associated with BMI only ($P = .011$). Tumor extracapsular extension was significantly associated with increased periprostatic fat volume ($P = .047$). Patients with less subcutaneous fat thickness (<2.4 cm) had significantly poor BCR–free survival ($P = .039$). Pelvic fat distribution, including pelvic fat volume, perirectal fat volume, and periprostatic fat volume, were significantly correlated with prostate cancer aggressiveness. Patients with less subcutaneous fat had an increased risk of BCR after radical prostatectomy.

**Abbreviations:** BCR = biochemical recurrence, BMI = body mass index, iPSA = initial prostate specific antigen, MRI = magnetic resonance imaging, PFV = pelvic fat volume, PPFV = peri-prostate fat volume.

**Keywords:** biochemical recurrence, body composition factors, fat distribution, magnetic resonance imaging, obesity, prostate cancer, subcutaneous fat, visceral fat

## 1. Introduction

Cancer is the leading cause of death worldwide and negative affects life expectancy.[1] In 2020, 1.4 million new cases of prostate cancer and 375,000 deaths were estimated worldwide, making it the second most common cancer and the fifth leading cause of cancer death among men.[1] The risk factors for prostate cancer include obesity, age, and family history. Obesity has been associated with prostate cancer in several studies,[2,3] whereas 3 meta-analyses[4–6] have reported a positive association between obesity and prostate cancer incidence. Moreover, obesity affects prostate cancer outcome. A systematic review and meta-analysis demonstrated a 21% increase in biochemical recurrence (BCR) (relative risk: 1.21) and a 15% increase in prostate cancer–specific mortality (relative risk: 1.15) following radical prostatectomy per 5 kg/m$^2$ increase in body mass index (BMI).[7]

Most studies have used BMI to define obesity severity.[3] However, BMI does not directly represent body composition and is therefore an inaccurate measure of obesity. In recent years, body composition, including fat and muscle distribution, has been studied to elucidate its role in prostate cancer. Hafe and colleagues suggested that visceral obesity, quantified using computed tomography, is a risk factor for prostate cancer.[8] Zimmermann demonstrated the effect of visceral fat volume and fat density on biochemical outcomes after radical prostatectomy and radiotherapy.[9]

Clinically, the extracapsular extension of prostate cancer cells into periprostatic fat is an adverse pathological feature related to a worse prognosis.[10] Van Roermund indicated

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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that periprostatic fat is directly correlated with prostate cancer aggressiveness and is more essential than BMI in the measurement of general obesity.[11] In previous studies, the pelvic fat tissue, part of visceral adipose tissue, of patients with prostate cancer was measured using computed tomography, transrectal ultrasonography, and magnetic resonance imaging (MRI).[12–15] Among them, MRI is a direct, quantitative measurement method to characterize pelvic fat tissue distribution.

In this study, we used preoperative MRI for cancer staging to calculate body composition and pelvic fat tissue distribution in patients with localized prostate cancer and investigate their effects on cancer aggressiveness and oncological outcomes.

## 2. Materials and Methods

### *2.1. Patient characteristics and treatment*

Between January 2009 and December 2018, 462 patients who were diagnosed as having localized prostate cancer underwent robot-assisted radical prostatectomy (RaRP) at Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan. Before the surgeries, all cases were reviewed in our multidisciplinary uro-oncological meeting, and the treatment plan decided was discussed with the patients. All patients had undergone a pretreatment MRI scan of the pelvis for staging and treatment planning purposes. Inclusion criteria included pathologically positive margins and no immediate adjuvant treatment, including radiotherapy, hormone therapy, or chemotherapy, after RaRP. One patient was lost to follow-up, resulting in 60 patients in the final analysis. Because prostate cancer has a relatively slow progression, we assumed that BCR would develop in more of these patients with adverse pathological features after RaRP. This research was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No.: 202000989B0). The requirement for Informed consent was waived due to the retrospective study design. All treatment methods were performed following the relevant guidelines and regulations.

### *2.2. Data collection and definitions*

Through patients' medical records, the following clinicodemographic characteristics were retrieved: age, body height, body weight, BMI, prostate volume, underlying disease, hemogram, biochemistry laboratory data, and prostate cancer–related parameters, including initial prostate-specific antigen (iPSA), bilateral Gleason score, TNM stage, BCR status, prostate-specific antigen level during follow-up, follow-up duration, and last follow-up status.

Pelvic fat distribution and body composition based on pretreatment MRI were measured by a single radiologist.

### *2.3. Image analysis*

***2.3.1. MRI technique*** MRI was performed using 1.5-T or 3-T systems. Axial, sagittal, and coronal T2-weighted images of the pelvis; axial T1-weighted images of the pelvis; axial contrast-enhanced T1-weighted images with fat suppression of the pelvis; and axial T2-weight images of the abdomen were routinely obtained from all patients. Only axial T1-weighted images of the pelvis and axial T2-weighted images of the abdomen were evaluated.

***2.3.2. MRI analysis*** MRI studies were anonymized and analyzed using OsiriX MD (version 10.0, Pixmeo SARL) by a radiologist blinded to all clinical information, except that these patients subsequently underwent RaRP.

On axial T1-weighted images of the pelvis, the regions of the pelvic cavity, prostate gland, seminal vesicles, bladder, perirectal space, and rectum were segmented manually from the prostate base to the apex. Their volumes were measured from consecutive images (Fig. 1).

Subsequently, pelvic fat volume (PFV), perirectal fat volume, and periprostatic fat volume (PPFV) were calculated using the following formulas:

1) PFV = pelvic cavity volume + bladder volume + prostate volume + seminal vesicle volume + rectal volume
2) Perirectal fat volume = perirectal space volume – rectal volume

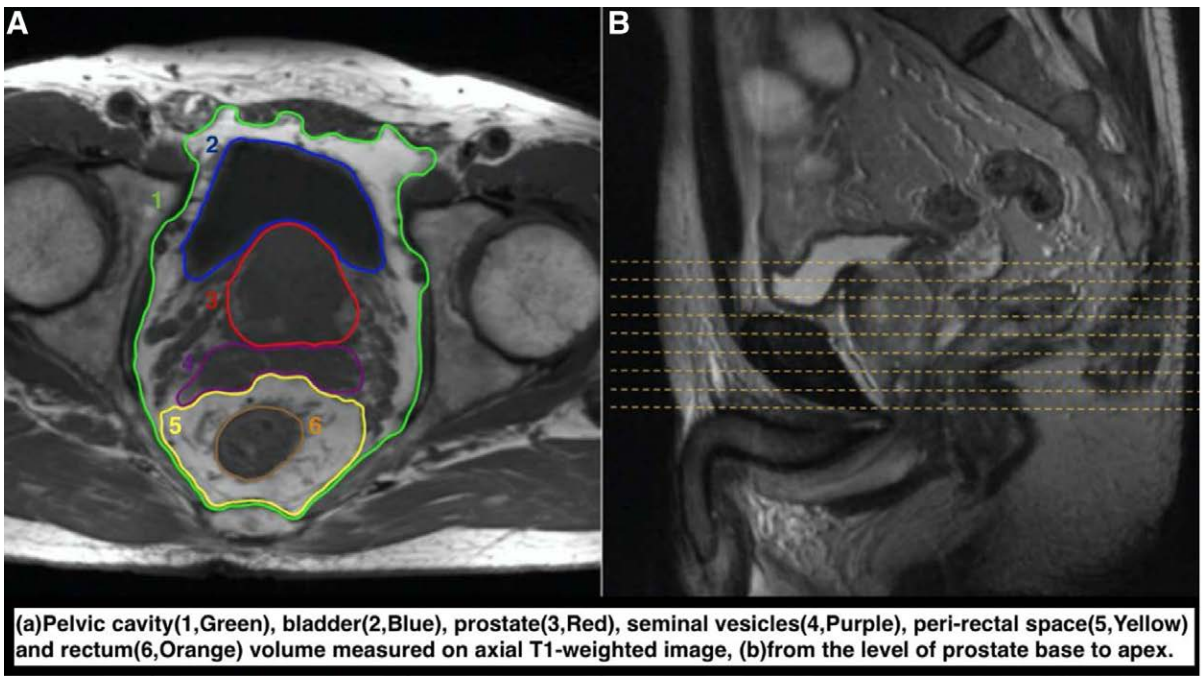


**Figure 1.** (a) Pelvic cavity (1, Green), bladder (2, Blue), prostate (3, Red), seminal vesicles (4, Purple), peri-rectal space (5, Yellow), and rectum (6, Orange) volume measured on axial T1-weighted image, (b) from the level of prostate base to apex.

3) PPFV = pelvic cavity volume – bladder volume, prostate volume, seminal vesicle volume, and perirectal space volume.

Subcutaneous fat thickness was determined by measuring the longest perpendicular distance from the skin to the rectus abdominis muscle on an axial T2-weighted image of the abdomen at the level of the umbilicus. In the same image, the psoas muscle area was measured through manual segmentation (Fig. 2).

*2.3.3. Ethics approval and consent to participate* This study has been conducted in accordance with the ethical principles mentioned in the Declaration of Helsinski (2013). This study was approved by Chang Gung Medical Foundation Institutional Review Board (IRB No.: 202000989B0).

### 2.4. Statistical analysis

The chi-square and independent *t* tests were used to compare intersubgroup differences. Pearson correlation analysis was used to estimate the correlation between all parameters. The Kaplan–Meier survival curve was performed to investigate survival. All statistical analyses were performed using SPSS v22.0. All tests were 2-tailed, with statistical significance considered at $P < .05$.

## 3. Results

### 3.1. Baseline characteristics

The mean age, BMI, and iPSA levels of the 60 patients were 65.2 years, 25.8 kg/m$^2$, and 17.5 ng/mL, respectively. Most patients had a Gleason score of 7 (45.0%) and a pathological stage of T2c (46.7%). The detailed clinical characteristics are listed in Table 1.

### 3.2. Body composition and tumor aggressiveness factors

The iPSA level was significantly high in patients with high volumes of pelvic (Pearson's $R = 0.393$, $P = .004$) and perirectal (Pearson's $R = 0.447$, $P = .001$) fat. Furthermore, patients with a high BMI had a high iPSA (Pearson's $R = 0.292$, $P = .027$). The detailed parameters are listed in Table 2.

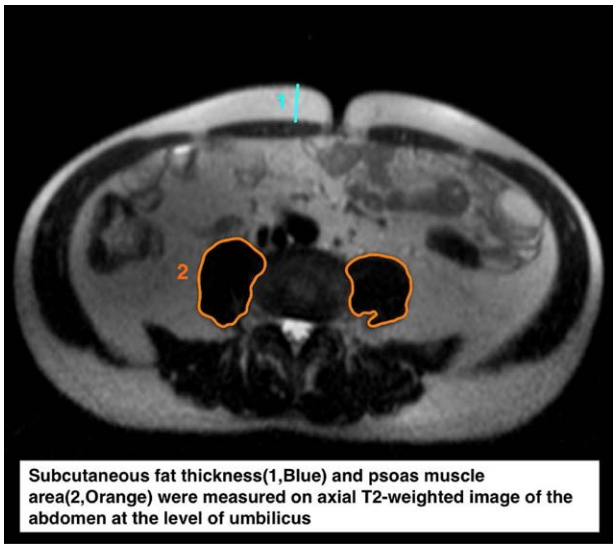


**Figure 2.** Subcutaneous fat thickness (1, Blue) and psoas muscle area (2, Orange) were measured on axial T2-weighted image of the abdomen at the level of umbilicus.

**Table 1**

**Patients' general characteristics.**

| Variables | | | Mean | SD | Range/ Percentage | |
|---|---|---|---|---|---|---|
| **Age** | | | 65.2 | 6.21 | 51-76 | Yr-old |
| **Body weight** | | | 70.1 | 10.1 | 53-94 | kilograms |
| **BMI** | | | 25.8 | 3.26 | 19.3-34.6 | |
| **TRUS volume** | | | 38.9 | 26.0 | 13-137 | grams |
| **iPSA** | | | 17.5 | 13.4 | 4.2-62.4 | ng/mL |
| **Gleason score** | 5 | 1 | | | 1.7% | |
| | 6 | 20 | | | 33.3% | |
| | 7 | 27 | | | 45.0% | |
| | 8 | 2 | | | 3.3% | |
| | 9 | 10 | | | 16.7% | |
| **Clinical T stage** | 1c | 1 | | | 1.7% | |
| | 2a | 13 | | | 21.7% | |
| | 2b | 1 | | | 1.7% | |
| | 2c | 28 | | | 46.7% | |
| | 3a | 11 | | | 18.3% | |
| | 3b | 5 | | | 8.3% | |
| | 4 | 1 | | | 1.7% | |
| **Nerve sparing** | No | 19 | | | 31.7% | |
| | Right only | 9 | | | 15.00% | |
| | Left only | 12 | | | 20.0% | |
| | Bilateral | 20 | | | 33.30% | |
| **Bladder neck sparing** | No | 44 | | | 73.30% | |
| | Yes | 16 | | | 26.70% | |
| **Body composition parameters** | | | | | | |
| **Subcutaneous fat thickness** | | | 2.49 | 1.63 | 1.23-10.00 | milliliter |
| **Left psoas volume** | | | 11.6 | 1.89 | 7.5-16.1 | milliliter |
| **Right psoas volume** | | | 11.6 | 2.24 | 6.4-16.6 | milliliter |
| **Total psoas volume** | | | 23.2 | 3.74 | 16.6-32.7 | milliliter |
| **Pelvic fat volume** | | | 111.9 | 47.7 | 38.1-254.4 | milliliter |
| **Peri-rectal fat volume** | | | 43.7 | 24.5 | 1.16-119.6 | milliliter |
| **Peri-prostate fat volume** | | | 68.2 | 30.1 | 22.7-164.3 | milliliter |

BMI = moby mass index, iPSA = initial PSA, TRUS volume = transrectal ultrasound of prostate volume.

The Gleason score was significantly high in patients with a high BMI (Pearson's $R = 0.334$, $P = .011$) and was not significantly correlated with any other body composition factors.

We examined whether the extracapsular extension of prostate cancer, which represents a locally advanced disease, was correlated with body composition parameters. PPFV was the only body composition parameter that was significantly high in those with tumor extracapsular extension ($P = .047$; Table 2).

### 3.3. Body composition and BCR–free survival

Prostate-specific antigen (≥0.2 ng/dL) has been used to detect biochemical failure after RaRP.

We divided each body composition factor into 2 groups based on its mean value. A log-rank test was performed to analyze the correlation between body composition factors and biochemical failure–free survival rate (Table 3). We observed that among the various body composition factors, only less subcutaneous fat thickness (<2.4 cm) was associated with significantly poor BCR–free survival (chi-square 4.245, $P = .039$, Fig. 3).

## 4. Discussion

Compared with BMI, body fat and lean tissue distribution have recently gained more interest in prostate cancer. Fat tissue is metabolically active and thought to play a major role in prostate

**Table 2**

**Tumor factors correlated with body composition factors.**

| iPSA | | Pearson correlation | | *P* value |
|---|---|---|---|---|
| BMI | | 0.292 | * | .027 |
| Subcutaneous fat thickness | | 0.041 | | .780 |
| Pelvic fat volume | | 0.393 | ** | .004 |
| Peri-rectal fat volume | | 0.447 | ** | .001 |
| Periprostate fat volume | | 0.259 | | .061 |
| Psoas muscle volume | | 0.130 | | .368 |
| Gleason score | | Pearson correlation | | *P* value |
| BMI | | 0.334 | * | .011 |
| Subcutaneous fat thickness | | -0.036 | | .806 |
| Pelvic fat volume | | 0.202 | | .146 |
| Peri-rectal fat volume | | 0.183 | | .189 |
| Periprostate fat volume | | 0.172 | | .219 |
| Psoas muscle volume | | 0.210 | | .143 |
| Extracapsular extension | | Mean | | *P* value |
| BMI | Yes | 25.98 | | .598 |
| | No | 25.51 | | |
| Subcutaneous fat thickness | Yes | 0.51 | | .962 |
| | No | 2.49 | | |
| Pelvic fat volume | Yes | 121.56 | | .109 |
| | No | 100.06 | | |
| Peri-rectal fat volume | Yes | 45.71 | | .490 |
| | No | 40.92 | | |
| Periprostate fat volume | Yes | 75.85 | * | .047 |
| | No | 59.14 | | |
| Psoas muscle volume | Yes | 24.11 | | .075 |
| | No | 22.20 | | |

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

carcinogenesis. Duong et al indicated that adipose tissue, particularly adipocytes, is a key actor in solid tumor progression.[16] Fat tissue, particularly visceral fat tissue, can produce multiple hormones and cytokines, such as tumor necrosis factor-α, interleukin-6, leptin, and adiponectin.[8,12] Adipocytokines secreted by visceral fat cells, steroid hormone disturbances, and increased levels of insulin or other hormones in visceral obesity may explain this association.

In our study, patients with a high BMI were significantly more likely to have high iPSA and Gleason scores, representing an increase in prostate cancer aggressiveness. Furthermore, patients with a high volume of pelvic and perirectal fat tissue had high iPSA, and a high periprostatic fat tissue volume was correlated with an increased rate of extracapsular extension. This finding is consistent with previous studies on the effect of periprostatic fat tissue on tumor aggressiveness. Woo et al reviewed 190 patients with prostate cancer who underwent MRI before radical prostatectomy and concluded that periprostatic fat thickness on MRI was significantly correlated with the Gleason score of prostate cancer and was an independent predictive factor for high-grade prostate cancer.[13] Similarly, Zhang et al evaluated the MRI of 184 patients with prostate cancer who had undergone radical retropubic prostatectomy and concluded that the periprostatic adiposity significantly affected the clinical stage and Gleason score of prostate cancer.[14] Bhindi et al determined that the amount of periprostatic fat estimated by transrectal ultrasonography is a predictor of prostate cancer, particularly high-grade prostate cancer.[15]

The mechanism underlying the relationship between PPFV and prostate cancer remains unclear. Periprostatic adipose tissue, a significant component of the prostate microenvironment, may be a crucial source of fatty acids and other mitogens and thereby influence prostate cancer pathogenesis and progression. Several recent studies have identified factors secreted from both periprostatic adipose tissue and prostate cancer that may mediate the 2-way communication between these intimately linked tissues.[17]

The importance of lean soft tissue distribution in prostate cancer was not observed in this study because psoas muscle volume did not appear to be correlated with tumor aggressiveness. However, studies have reported that muscle mass is associated with survival in patients with various types of solid tumors. Pak et al retrospectively reviewed 2042 patients who underwent radical prostatectomy for prostate cancer and concluded that low muscle mass may be associated with increased risks of recurrence and mortality, regardless of BMI.[18]

In our study, less subcutaneous fat thickness was the only body composition factor significantly correlated with an increased BCR after RaRP. PFV and PPFV were significantly correlated with prostate cancer aggressiveness but not with BCR–free survival. The inconsistent result that less subcutaneous fat correlated with low BCR emerged as the topic of obesity paradox,[19] which suggests that obesity has a protective effect. Recent studies have indicated that patients with cancer having a lower than normal BMI (or those with weight loss) have worse outcomes than patients with obesity.[20] This phenomenon was first described in cardiovascular and diabetes research. Schiffmann et al recorded the obesity paradox phenomenon in patients with prostate cancer, where a high BMI (≥30) was associated with a decreased risk of metastases after radical prostatectomy.[21] Many hypotheses exist to explain the obesity paradox, but they remain controversial.

Our study has some limitations. First, the relatively small sample size may have led to increased variability and age bias. Second, only patients with prostate cancer who underwent RaRP with positive surgical margins were enrolled because they were regarded as susceptible to BCR with adverse pathological features, thus facilitating our observation for oncological outcome. Further studies should clarify the effects of these body composition factors on patients with different stages of prostate cancer and receiving different treatment modalities.

## 5. Conclusions

In addition to high BMI, increased fat volumes of the pelvic, perirectal, and periprostate regions were associated with aggressive prostate cancer. Patients with less subcutaneous fat experienced significantly poor BCR–free survival after RaRP, whereas BMI and other body composition factors were not significantly correlated with BCR.

**Table 3**

**Analysis of body composition factors for biochemical failure free survival.**

| | Cutoff (Mean) | Log rank test (Mentel-Cox) | | |
|---|---|---|---|---|
| | | Chi-Square | | *P* value |
| BMI | 25.8 | 0.266 | | .606 |
| Subcutaneous fat thickness | 2.4 | 4.245 | ** | .039 |
| Pelvic fat volume | 111.9 | 0.252 | | .616 |
| Peri-rectal fat volume | 43.7 | 0.035 | | .851 |
| Periprostate fat volume | 68.2 | | | |
| Psoas muscle volume | 23.2 | 0.268 | | .605 |

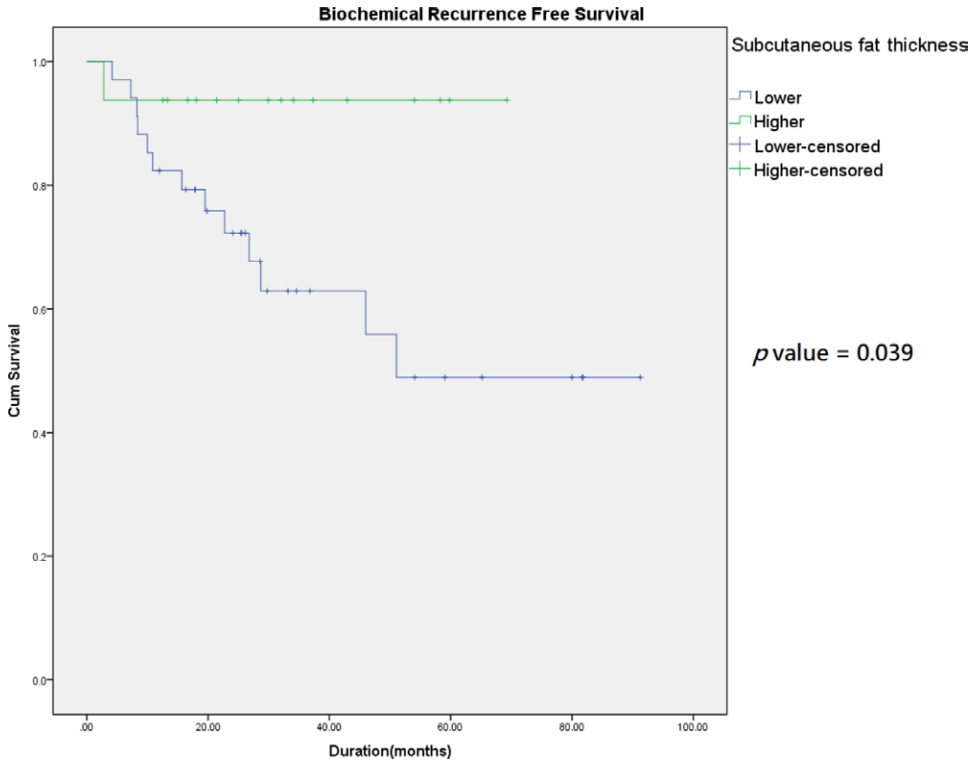


Figure 3. Less subcutaneous fat thickness (<2.4 cm) was associated with significantly poor biochemical recurrence–free survival (chi-square 4.245, $P = .039$).

## Authors' contributions

**Conceptualization:** Yu-Hsuan Chien, I-Hung Shao, Ming-Li Hsieh.
**Data curation:** I-Hung Shao.
**Formal analysis:** Yu-Hsuan Chien, I-Hung Shao, Ting-Wen Sheng, Li-Jen Wang.
**Methodology:** Yu-Hsuan Chien,I-Hung Shao, Ting-Wen Sheng, Li-Jen Wang.
**Project administration:** Yu-Hsuan Chien, I-Hung Shao.
**Supervision:** I-Hung Shao, Ming-Li Hsieh, Ying-Hsu Chang, Cheng-Keng Chuang, See-Tong Pang, Chun-Te Wu.
**Visualization:** Yu-Hsuan Chien.
**Writing – original draft:** Yu-Hsuan Chien.
**Writing – review & editing:** I-Hung Shao.

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