

## Comparison between commonly practised techniques of flexor tendon repair considering the preferences of surgeons in Malaysia with biomechanical analysis

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### ABSTRACT

**Background:** Flexor tendon injuries are among the most challenging Orthopaedic conditions to manage. Early repair and physical therapy are crucial for good outcome as well as the repair method.

**Objective:** This study aims to explore the surgical preference of orthopaedic and hand surgeons of Malaysia integrated with biomechanical analysis of the common repair techniques to ensure quality and early outcome of various techniques.

**Methods:** A survey was distributed among the orthopaedic and hand surgeons at annual Orthopaedic conference in 2019 and Hand surgery conference in 2021 to explore their preferences of flexor tendon repair. For biomechanical study, forty tendon samples were obtained from the amputated lower limbs and were repaired using one of the four popular 4-strands repair methods. Samples were then biomechanically tested. Three variables were monitored, core suture placement time, force required for 2-mm gap creation, and ultimate tensile strength. Statistical analysis was conducted to examine an association between core tendon repair techniques and the load required to cause repair failure.

**Results:** Among the respondents of the survey, there was no consensus for the technique of the repair, however most of the respondents utilized a 4-strand technique using 4/0 Prolene suture. Inner and outer Kessler method was found to be the quickest to place at  $5.77 \pm 0.55$  min. The Adelaide (AD) method required the largest maximum force to fail at  $42.07 \pm 14.57$  N and the highest force for 2 mm gap at  $29.07 \pm 15.43$  N.

**Conclusions:** Flexor tendon repair is a technically demanding procedure requiring a balance between surgeons' skill and technique and strength of the repair. As all 4-strands repairs can withstand the 10 N load generated by mildly resisted active flexion and extension of the fingers, post operative therapy could be launched immediately after the repair.

### 1. Introduction

Management of flexor tendon injuries (FTI) has made significant progress, yet they remain among the most difficult orthopaedic conditions to treat.<sup>1</sup> FTI occurs most commonly by laceration, FTI's have a male predominance with the age group 20–29 years accounting for the largest incidence.<sup>2</sup> Work-related injuries account for ~25 % of acute traumatic FTI. Among different occupations, construction workers and

extraction workers account for 44 %, food preparation and serving staffs account for 14 %, and transportation workers and material movers each account for 12 % of acute traumatic FTI.<sup>3</sup> A study by O'Sullivan and Colville reported that the complicated lacerations of flexor tendons ranked second to amputation injuries in terms of cost and number of work days lost.<sup>4</sup>

Complete transection of the flexor tendon does not heal spontaneously; hence, early meticulous repair is the typical treatment for a

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complete cut. As the flexor tendon glides through a narrow constrictive sheath, pulley system - in zone I and II, and through carpal tunnel in zone IV, any bulky repair may result in limited motion. An ideal primary repair of flexor tendons should comprise of an easy placement of the sutures in tendon, secured knots, smooth junctions, minimal gapping at repair site, minimal interference with tendon vascularity, and sufficient strength throughout the healing process to permit the full range of motion.<sup>5</sup> Since the outcome of the repair largely depends on adequate post-operative management, post-repair therapy needs to be well balanced. An early mobilisation surely prevents the adhesion formation and improves gliding, yet risks tendon rupture.<sup>5</sup> The early active mobilisation stimulates the healing as well. During the immediate post operative period, the strength of the repair depends only on the suture material and the technique used; hence, both the suture material and repair techniques are crucial for the survival of the repair at this stage. Current evidence suggests that ideal core suture materials should have a high tensile strength, be inextensible, cause no tissue reaction, and be easy to handle and place knots.<sup>6</sup> Theoretically, increasing the size of the core suture and number of the strands will enhance the strength of the repair. Though it is not practical for the flexor tendons as they need to be glided through the pulley or carpal tunnel.

Considering all these factors, flexor tendon repair techniques vary among the surgeons. Interestingly, there has been documentation of different repair techniques being preferred over others when the country of practise is accounted for. For instance, a 2014 study showed that in the UK, the preferred technique of flexor tendon repair was 2-strand Kessler repairs (prevalence 36 %) even though prior studies have shown that a 2-strand repair is biomechanically inferior to four or more strand repair,<sup>7</sup> and the most commonly used sutures are Prolene (Ethicon, Edinburgh), Ethibond (Ethicon) and Ticron (Tyco Healthcare, Gosport, UK).<sup>7</sup> A very recent (2024) study showed that current practice in the UK has shifted toward a preference for the cruciate technique (28 %) and the Adelaide technique (21 %).<sup>8</sup> In a 2019 Turkish study, comprising mostly of plastic surgery trained hand surgeons, the modified Kessler technique was preferred by 65 % of their respondents.<sup>9</sup> A Malaysian study was published in 2022, where Orthopaedic surgeons as well as the residents were included for a survey on zone II tendon repair technique. This study showed a preference toward the modified Kessler followed by the Adelaide repair at 33.1 % and 27.9 % respectively.<sup>10</sup> The present study aims to explore the surgical preferences for flexor tendon repair as a whole along with the commencement of post operative therapy among the orthopaedic and hand surgeons in Malaysia integrated with the biomechanical analysis of the common techniques to validate the quality and outcome of different techniques.

## 2. Materials and methods

### 2.1. Survey among the surgeons

Ethical approval was obtained from the Ministry of Health of Malaysia with an approval code of NMRR-17-3424-39243 (IIR). A questionnaire was distributed among the orthopaedic and hand surgeons during the Malaysian Orthopaedic Association Annual Scientific Meeting 2019 and the Malaysian Society of the Surgery of Hand (MSSH) Annual Meeting 2021. The questionnaire along with a consent form was also emailed and sent via instant messaging platform—WhatsApp to all the members of MSSH and requested to get their response within a month if they did not fill up the questionnaire before. The questionnaire consisted of 24 multiple choice questions (MCQ) for objective assessment concerning the treatment selections and techniques of the FTI repair. A total of 85 completely answered responses from the general orthopaedic and hand surgeons were included in this study. Partially completed questionnaires and the questionnaires filled out by the residents or non-orthopaedic or non-hand surgeons were excluded from this study.

### 2.2. Tendon specimen

After obtaining ethics committee approval (UKM PPI/111/8/JEP-2019-320) and patients' consent, a total of 40 healthy intact similar sized (50 mm × 10 mm) extensor and flexor tendon samples were obtained from the amputated part following trans-tibial amputations. Tendons were considered healthy based on four criteria: (i) glistening white color, (ii) not friable, (iii) having an intact and preserved tendon sheath, and (iv) no signs of infection such as necrosis or pus. Only healthy tendon specimens following the four criteria were considered in this study. The harvested tendons were immediately wrapped in phosphate buffer saline (PBS) soaked gauzes to keep it moist and stored at -20 °C whilst waiting for the experiment.

### 2.3. Tendon repair techniques

On the day of the experiment, tendons were thawed keeping on ice packs and transected into two parts. Repair was done immediately following the four different 4-strands repair techniques, (i) Inner and Outer Kessler (IO) - double knot, (ii) Modified Kessler with Single Knot (SK), (iii) Double knot side by Side Kessler (SS) and (iv) Adelaide Technique (AD) as shown in Fig. 1. Ten samples were considered in each repair group. During repair, 4-0 Prolene (ETHICON, New Jersey, USA) was used for the core suture, and the core sutures were placed 7-10 mm from the injury site. Lock loop or cross lock anchors were made with 2 mm tendon purchase. And 6-0 Prolene (ETHICON, New Jersey, USA) sutures were used for simple running epitendinous repair. Epitendinous repair was done with the 2 mm tendon purchase for 8-10 times. All the tendons were repaired by a single orthopaedic fellow with four years of training, using the aid of loupes with X3.5 magnification. Time taken for the core sutures placement was recorded for all the techniques. Markings were made at 1.5 cm on each side of the repair with a skin marker, and repaired samples were again kept into the -20°C freezer until the day of the biomechanical testing (see Fig. 2).

### 2.4. Biomechanical testing

On the day of the biomechanical test, the repaired tendon samples were thawed again on ice pack and kept moist throughout the testing with PBS saline spray. The tensile tests were conducted with 3365 Universal Testing Machine (UTM) (INSTRON, Massachusetts, USA) with load cell of 2 kN and Bluehill 2.0 software. Custom-designed stainless-steel clamps were used to prevent tendon slippage. Clamps were placed at 1.5 cm from the repair site (as previously marked) with a pressure of 5 bar and a preload of 2 N was applied to eliminate a slack from the specimen if there is any. The tensile test was conducted with a strain rate of 10 mm/min until failure. Two mm gap strength and ultimate tensile strength were calculated in this study for the biomechanical characterization.

Statistical analyses were performed using IBM SPSS version 29.0. All numerical data were presented as *mean*±*SD*. Due to the relatively small number of samples and nonnormality of the data, nonparametric Kruskal-Wallis test was conducted for general comparison and Mann-Whitney *U* test was used for inter group comparison. A significance level was set at *p* < 0.05 and was employed for all tests.

## 3. Results

### 3.1. Survey among the surgeons

A demographic breakdown of the survey included 85 respondents which included 69.4 % general orthopaedic surgeons, and 30.6 % hand surgeons. The group of respondents aged 30-40 comprised 41 % of respondents, the next largest group was those aged between 41 and 50 years accounting for 28.2 % of respondents (Table 1). The location of practice included 48.2 % working at public hospitals, 31.8 % working in

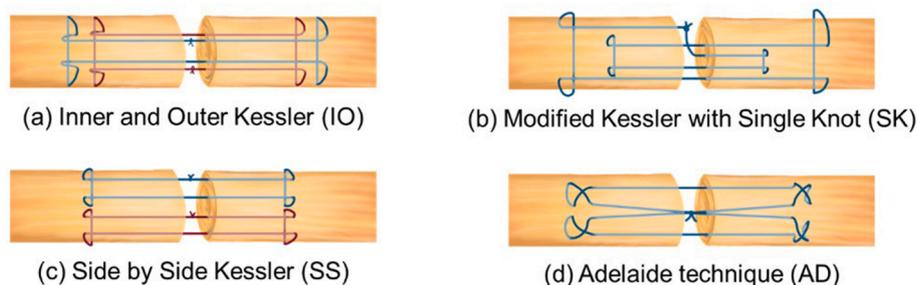


Fig. 1. Different tendon repair techniques considered in this study.

private hospitals, and 20 % working in university hospitals (Table 1).

General anaesthesia (GA) accounted for more than half (56.5 %) Of the preferred anaesthesia methods for flexor tendon repairs. The other routes used included regional (15.3 %), local (8.2 %), and wide-awake local anaesthesia no tourniquet - WALANT (5.9 %). The remaining surgeons preferred more than one route of anaesthesia or had no preference (Table 1).

Among the respondents, there were three top Corner repair techniques that were preferred which included SK (27.2 %), AD (23.5 %), and SS (20 %) (Table 1). The number of core strands used in the repair of flexor tendons included a strong preference for the four-strand technique (61 %), followed by 2-strand (14.1 %), and 6-strand (10.6 %). The other respondents multiple preferences or no preference (Table 1).

The top three preferred suture sizes were 4/0 (63.5 %), 3/0 (14.1 %) and 5/0 (4.7 %) (Table 2). Most respondents preferred to use Prolene suture accounting for 72.9 %, followed by Supramid (10.6 %) and Ethibond (3.5 %) (Table 1). Furthermore, 90.6 % of the respondents chose to do an epitendinous repair and the preferred suture size for the epitendinous repair was 6/0 (55.9 %), followed by 5/0 (21.2 %) (Table 1). The most preferred suture type for the epitendinous repair was Prolene as well (72.9 %).

For zone II injury, 23.5 % of the respondents preferred to repair flexor digitorum profundus (FDP) tendon only, whereas 37.6 % preferred to repair both FDP and flexor digitorum superficialis (FDS), and 34.1 % repair FDP with one slip of FDS (Table 1).

Immediate post operative therapy with passive flexion was preferred by 57.6 % and 31.8 % initiate therapy with passive flexion at 2 weeks. Active motion was preferred to be initiated at two weeks by 32.90 % of respondents and at four weeks by 31.8 % of respondents. Of the respondents, 21.2 % initiate active motion immediately after the surgery (Table 1).

### 3.2. Biomechanical analysis of the repair techniques

The force vs displacement graphs obtained from the tensile testing for each of the tendon repair techniques are shown in Fig. 3. The maximum force required for repair failure represents the ultimate tensile strength (N), and the 2-mm gap force was indicated on the graph. In these graphs, suture rupture was denoted by a sudden drop in the tensile load.

Three variables were calculated. This included the time to place the core sutures, force required to create a 2-mm gap, and the ultimate tensile strength. The time required to perform each repair technique included the IO method which took the shortest time,  $5.77 \pm 0.55$  min, to complete the repair, whereas SS method took the longest,  $9.00 \pm 2.06$  min (Table 2).

The mean force generating 2-mm gap at the repair site varies for each technique. The AD method required the most force of  $29.07 \pm 15.43$  N, and the IO method required the least force of  $13.76 \pm 8.02$  N to create 2-mm gap.

The highest ultimate tensile strength was achieved by the AD method at  $42.07 \pm 14.57$  N, and the lowest (weakest) was exhibited by the IO

method at  $24.00 \pm 9.25$  N.

The comparison of all these three variables between the repair techniques have been shown in Table 3. The median of each technique was statistically analysed with the non-parametric Kruskal-Wallis test as well as with the Mann-Whitney *U* test. All the three parameters—time taken for the core suture ( $p = 0.007$ ) ( $p = 0.007$ ), force generating 2 mm gap ( $p = 0.015$ ) ( $p = 0.015$ ), and the ultimate tensile strength ( $p = 0.001$ ) ( $p = 0.001$ ) were statistically significant.

The differences in time taken to place the core sutures was found to be statistically significant when the SS and IO methods were compared ( $p = 0.001$ ) and the AD and IO methods were also found to be statistically significant ( $p = 0.001$ ). For the 2 mm gap force, statistically significant difference ( $p = 0.020$ ) was observed when the SS and AD methods were compared, and when the IO and AD methods were compared. When the ultimate tensile strength was compared, statistically significant difference was observed when comparing the AD and IO methods (Table 3). From the subjective assessment of the biomechanical test results along with the statistical inferential methods, the best repair technique is the AD method in terms of strength.

### 4. Discussion

Functional restoration following the flexor tendon repair has been a great challenge for the surgeons.<sup>11</sup> Researchers have been striving to prevent the disruption of the surgically repaired tendons during the early weeks of the repair. An ideal repair should provide adequate strength to prevent gap formation and failure of the repair, while causing minimal tendon damage and tissue reaction.<sup>12</sup>

General anaesthesia (GA) is the most widely used anaesthetic route for ambulatory surgery<sup>13</sup> the anaesthesiologists are usually more confident in giving GA.<sup>14</sup> Current short-acting GA agents generate significantly fewer adverse effects, a better recovery profile, higher patient satisfaction, and are more cost-effective.<sup>15</sup> However, several studies have demonstrated that the utilization of regional anaesthesia (RA) provided better early pain control. There were also fewer adverse effect and patients were discharged from the hospital sooner.<sup>16</sup> Other studies have found that for patients that have hand surgery where RA is utilized, they are less likely to require analgesic and antiemetic medication during the recovery period.<sup>17</sup> In addition, the use of a forearm or arm tourniquet provide better visualisation of the surgical field; hence, is a common and universally accepted practice in hand surgery.<sup>18</sup> According to the survey analytics, more than half of the respondents preferred GA along with the tourniquet for the FTI repair.

As per the conducted survey, SK was the most popular core suturing technique of the tendon repair (27.1 %), followed by the AD (23.5 %) technique among the surgeons in Malaysia. The popularity of modified Kessler (SK) found in this study is aligned with prior study conducted in the United States.<sup>19</sup> It is probably because SK is a relatively simpler technique compared with others. A meta-analysis demonstrated that adhesion formation was 57 % lower when the SK technique is used.<sup>20</sup>

Biomechanical analysis demonstrated that AD repair was the most reliable suture techniques and even stronger than the popular Modified

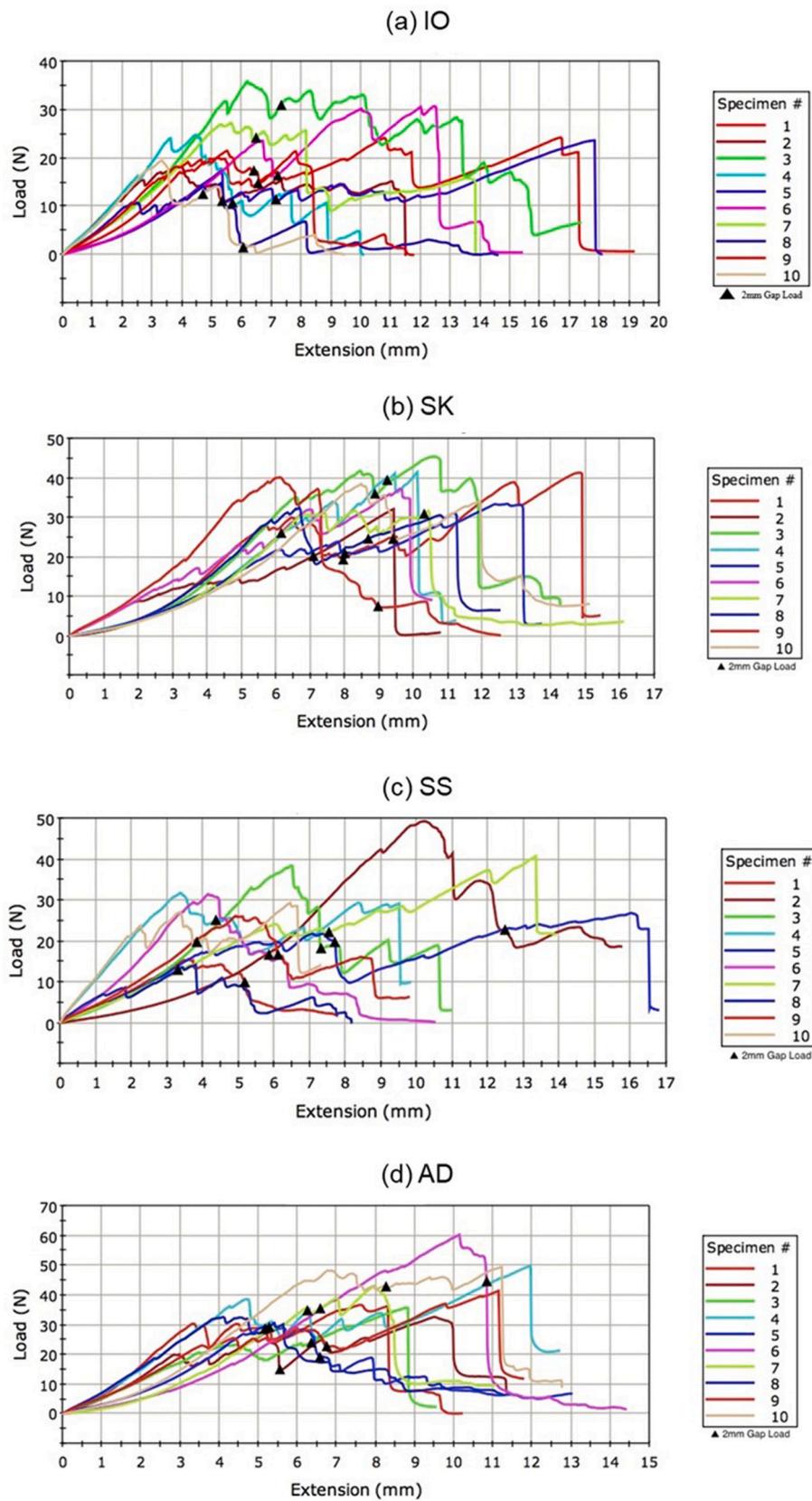


Fig. 2. Tensile force vs displacement plot for different repair techniques (a) IO, (b) SK, (c) SS and (d) AD. For each repair technique the sample size was 10.

**Table 1**  
Demographics and surgical preferences of survey respondents.

Characteristics	Total, n (%)
Total survey participants	85
Age (in years)	85
<30	5 (5.9)
30–40	40 (47.1)
41–50	24 (28.2)
>50	16 (18.8)
Practice setting	85
Government Hospital	41 (48.2)
Private Hospital	27 (31.8)
University Hospital	17 <sup>20</sup>
Anaesthesia Preference	85
General	48 (56.5)
Regional	13 (15.3)
Regional, General	7 (8.2)
Don't know	2 (2.4)
Local	7 (8.2)
Local, Regional, General	2 (2.4)
WALANT	5 (5.9)
WALANT, General	1 (1.2)
Tourniquet Preference	85
Yes	72 (84.7)
Don't Know	5 (5.9)
No	8 (9.4)
Core repair technique	85
Modified Kessler	23 (27.1)
Adelaide	20 (23.5)
Double Modified Kessler	17 (20.0)
6 Strand	1 (1.2)
Adelaide, Lim-Tsai	1 (1.2)
Don't know	3 (3.5)
Double Modified Kessler, Adelaide	2 (2.4)
Double Modified Kessler, Lim-Tsai	2 (2.4)
Lim-Tsai	6 (7.1)
Modified Kessler, Adelaide	8 (9.4)
Modified Kessler, Double Modified Kessler	1 (1.2)
Modified Kessler, Double Modified Kessler, Adelaide	1 (1.2)
Number of core strands	85
2-strand	9 (10.6)
2-strand, 4-strand	3 (3.5)
4-strand	51 (60.0)
4-strand, 6-strand	6 (7.1)
6-strand	12 (14.1)
Don't Know	4 (4.7)
Core repair suture size	85
3/0	12 (14.1)
3/0, 4/0	4 (4.7)
4/0	54 (63.5)
4/0, 5/0	3 (3.5)
4/0, 6/0	1 (1.2)
5/0	3 (3.5)
5/0, 6/0	1 (1.2)
6/0	4 (4.7)
Don't Know	3 (3.5)
Core repair suture material preference	85
Prolene	62 (72.9)
Supramid	9 (10.6)
Braided polyester tend-loop, 4.0.	1 (1.2)
Don't Know	2 (2.4)
Ethibond	3 (3.5)
Prolene, Bbraun looped	1 (1.2)
Prolene, Supramid	1 (1.2)
Prolene, Ticron	1 (1.2)
Prolene, Ticron, Supramid	2 (2.4)
Ticron	1 (1.2)
Ticron, Supramid, Ethibond, Nylon	2 (2.4)
Epitendinous repair preference	85
Yes	77 (90.6)
Don't Know	2 (2.4)
No	6 (7.1)
Zone II repair preference	85
Repair both FDP & FDS	32 (37.6)
Repair FDP only	20 (23.5)
Repair FDP with 1 slip of FDS	29 (34.1)
Don't Know	4 (4.7)

**Table 2**  
The basic description of each suture technique according to the time, 2 mm gap strength, and the ultimate tensile strength.

Variable	Type of suturing done			
	IO n=10	SK n=10	SS n=10	AD n=10
Time (min) (median ± IQR)	5.77 (0.55)	9.00 (2.06)	7.37 (1.03)	7.02 (1.48)
2 mm gap strength N (median ± IQR)	13.76 (8.02)	24.62 (12.16)	19.07 (6.53)	29.07 (15.43)
Ultimate tensile strength N (median ± IQR)	24.00 (9.25)	37.67 (8.89)	30.39 (15.59)	42.07 (14.57)

Kessler techniques. Lahey, and Becker mentioned that AD repair had small displacement, high stiffness, and almost no suture pull-out.<sup>21</sup> However, it has some disadvantages too such as the presence of exposed suture material on the surface of the tendon, more tissue handling from placing the cross-locks and to ensure tendon ends are well approximated, and the lack of additional tensioning of the repair at the time of final knot tying.<sup>22</sup>

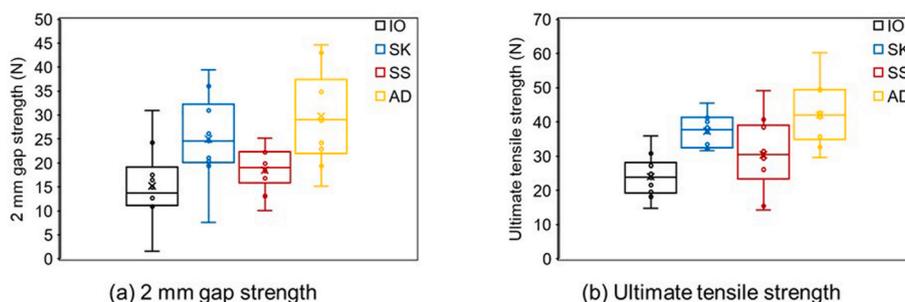
The survey part of the study found that the top preference of core suture technique was 4-strand among Malaysian surgeons. A prior study demonstrated that 2-strand repair had significantly greater gap formation with force compared with 4- and 6-strand repairs, while 6-strand had substantially higher tensile strength than 2- and 4-strand methods. However, the 6-strand repair is potentially associated with more adhesion formation due to extensive tendon manipulation, resulting in more exposed sutures on the tendon surface.<sup>23</sup> A biomechanical study, with rabbit model demonstrated that 4-strand core suture improved flexor tendon repair in comparison with the 2-strand repair technique.<sup>24</sup>

As per the conducted survey, majority of the respondents preferred to use Prolene 4/0 for the core suture. Though the size of the core suture has direct impact on the tensile strength, the work of flexion increases significantly when the suture size increases from 4/0 to 2/0.<sup>25</sup> Therefore, the surgeons need to maintain a balance between the tensile strength and work of flexion. Suture material plays a vital role in the final outcome of the tendon repair.<sup>26</sup> This study also showed all the polyester fibre-based sutures performed better on tests.

A meta-analysis of 29 studies demonstrated that neither the core suture technique did not influence the rupture rate. This same study found that the use of an epitendinous suture did not influence the rupture rate. However, the presence of an epitendinous suture reduces the rate of re-operation by 84 %.<sup>20</sup> Epitendinous-first flexor tendon repair significantly reduces the mean gliding resistance, ease the placement of core sutures, and cause decreased bunching.<sup>27</sup> Sue et al. recommended a 6/0 polypropylene suture to be used for the epitendinous repair,<sup>28</sup> which is aligned with our survey result.

Studies are conducted to examine the force experienced by active and passive motion of the flexor tendons of the hand. One study showed that passive motion produces 2–4 N of force. Mild resisted active motion produces up to 10 N of force, moderate resistance produces up to 17 N of force, and strong grasp produces up to 70 N of force.<sup>29</sup> Comparing the different repair techniques, the stronger repair techniques accommodate for a larger percentage of the force exerted on the tendons.

As passive and active mildly resisted flexion generates 2–4 N and 10 N respectively and all 4-strand repairs can withstand 10 N of force generated with mildly resisted motion, after 4 strand repair post operative therapy could be started immediately. Our survey showed that majority of the surgeons prefer early post operative therapy starting immediately for passive motion and at 2 weeks postoperatively for



**Fig. 3.** Box-whisker plot showing the distribution of 2 mm gap strength (a) and ultimate tensile strength of different repair techniques. For each repair technique the sample size was 10.

**Table 3**

The statistical comparison of each suture technique according to the time, 2 mm gap strength, and ultimate tensile strength.

Variable	Comparison among groups		
	Overall p value	Significant comparison	Comparison p value
Time in minutes	0.007	Side by side and Inner outer Adelaide and Inner outer	0.001 0.001
2 mm gap strength N	0.015	Side by side and Adelaide Inner Outer and Adelaide	0.020 0.020
Ultimate tensile strength N	0.001	Adelaide and Inner Outer	0.001

active motion which is aligned with the biomechanical tests.

Method of zone II flexor tendon repair is still controversial. In our study, 37.6 % respondents preferred to repair both FDP and FDS, and 34.1 % preferred to repair the FDP with one slip of FDS. Repair of both tendons in zone II is ideal, but technically demanding. Many hand surgeons preferred to repair the FDP and a slip of FDS instead of both the slips of FDS as it could result in overcrowding within the sheath and pulleys and compromise the outcome.<sup>30</sup> Repair of the FDP tendon alone is easy, technically less demanding and shows good outcome as well. However, it carries a significant risk of failure if the repaired tendon breaks down during the post operative physiotherapy.<sup>5</sup>

Our study has some limitations. In the questionnaire, there was no question related to their current practice like how many flexor tendons repair they perform every month? This information could provide a clearer picture of the respondents' real experience of flexor tendon repair. For the biomechanical study, the results should be interpreted with caution as the sample size were relatively small, and the suturing was done by a single surgeon who might have preference and familiarity of doing repair with a particular technique.

**5. Conclusions**

Flexor tenon repair is a technically demanding procedure. Repair technique as well as the post-operative therapy both influences the outcome. This study compares the surgeons' preference with the biomechanical analysis between the common flexor tendon repair techniques and showed that 4-strand Double Modified Kessler with the single knot variant which was the most popular technique among the Malaysian surgeons was slightly lower in strength to the Adelaide cruciate locking method which was proved as the strongest. For surgeons who have trouble mastering the Adelaide technique, this could be an acceptable alternative. However, training different techniques specially AD should be addressed during the orthopaedic residency period and could be remedied by organizing workshops and training during the

time of the residency.

**CRedit authorship contribution statement**

**Shalimar Abdullah:** conceived and supervised the study, takes responsibility for the integrity of the work, from inception to finished article. **Rahul Lingam:** performed experiments, analysed data, and compiled figures, wrote the manuscript. **Walter Gryczewski:** performed experiments, analysed data, and compiled figures, wrote the manuscript. **Md Rayhan Ali Mollah:** performed experiments, analysed data, and compiled figures, wrote the manuscript. **Elaine Soh:** performed experiments, analysed data, and compiled figures. **Jamari Sapuan:** conceived and supervised the study. **Tanvir Rahman Faisal:** conceived and supervised the study, the integrity of the work, from inception to finished article, All authors contributed to the article, interpreted the data, revised the manuscript, and approved the submitted version, Authors confirm that neither this manuscript, nor one with substantially similar content, has been submitted, accepted or published elsewhere (except as an abstract). **Ahmed Suparno Bahar Moni:** conceived and supervised the study.

**Patient consent**

Informed consent was obtained from all the participants for the survey.

**Ethical statement**

Ethical approval was obtained from the Ministry of Health of Malaysia with an approval code of NMRR-17-3424-39243 (IIR).

**Role of funding source**

It is a non-funded study.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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