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Risk factors of second surgery for adjacent segment disease following anterior cervical discectomy and fusion: A 16-year cohort study

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ABSTRACT

Background: Although the incidence of second surgery for adjacent segment disease (ASD) after anterior cervical discectomy and fusion (ACDF) has been reported, its risk factors remain elusive. Few studies have had a sufficiently large number of patients, long follow-up time, and high follow-up rate for investigation. To identify non-surgical risk factors of second surgery for ASD following ACDF, the study used a national cohort with comprehensive follow-up.

Materials and methods: All second ACDF surgery after one year from the first ACDF were identified as a consequence of ASD that required another surgery. A multivariate competing risk survival model, Kaplan-Meier survivorship, and average time to events were calculated.

Results: Among 38,149 patients who had the first ACDF, 1,092 (2.9%) later (mean 4.66 years) received a second ACDF surgery, during the nearly-perfect follow-up of 16 years. Young age and psychiatric disorders were independent risk factors. Patients who were aged under 40, 50, 60 and 70 years were, respectively, 4.56, 4.09, 3.09 and 2.17 times more likely than those older than 70 years. Also, patients with depression or psychoses were, respectively, 1.42 and 1.45 times more likely to have second surgery for ASD. (all $p < 0.05$).

Conclusion: Young age and psychiatric disorders are independent risk factors of second ACDF surgery for ASD. Personalized strategies to ameliorate or postpone the development of ASD are therefore warranted for patients who need ACDF surgery.

1. Introduction

Adjacent segment disease (ASD) has reportedly been an issue after surgery for spinal fusion since a number of patients required a second surgery few years afterward. Although some experts still consider ASD as a consequence of natural history, much literature attributes it to the compensatory increase of workload on the neighboring disc segment after vertebral arthrodesis [1–4]. The most frequently cited incidence of ASD after anterior cervical discectomy and fusion (ACDF) was 2.9% per year, which was derived from a retrospective cohort of 374 patients [5]. There was also a large cohort study, which included 19,385 ACDF patients, that demonstrated that within a decade a considerable portion (5.6%) of these ACDF patients received a second ACDF surgery due to ASD [6]. The same study also suggested that younger male patients were more likely to receive a second ACDF surgery than older women. Although there were many other speculations on the risk factors of ASD, including surgical techniques and instrumentations applied, there was a paucity of data on the risk factors of ASD as well as its prediction after ACDF, one of the most satisfying neurosurgical procedures.

Risk factors of a second surgery for ASD after spinal fusion surgery remain elusive due to the difficulty of investigation. Since the development of clinically significant ASD frequently requires a long time period, a longitudinal cohort of patients with high rates of follow-up is necessary for detection. The present study thus used for analysis a national cohort (from 1997 to 2013) of patients who underwent ACDF. The cohort was uniquely ideal for such an investigation because the national health insurance system in Taiwan monopolistically covers all surgery and subsequent management, which automatically allowed for a complete follow-up. No matter where the second operation took place, all patients and their comorbidities could be traced. Furthermore, the study captured the most clinically significant ASD by identification of the second ACDF surgery. Following the first ACDF, ASD could come

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in various degrees of severity and thus were managed with a variety of strategies. For instance, minor ASD could be completely asymptomatic, and only detectable by magnetic resonance images (MRIs). In contrast, severe ASD that caused serious neurological problems would usually lead to a second ACDF surgery.

To identify the risk factors, the study defined patients with ASD as those who required a second ACDF surgery. By that definition, only severe ASD would be included and thus it was the lowest estimation. Those minor, undetected, or less symptomatic cases of ASD would not be identified. Although there was a lack of unanimous determination of ASD in the literature, in common practice a second ACDF could be considered the most definite diagnosis and treatment of ASD after the first ACDF. The model, using a second ACDF as a proxy to identify severe ASD requiring surgery, has also been testified and published for calculation of such incidences of ASD [6]. Therefore, the model should also be sound for the investigation of risk factors of ASD after ACDF. Since there have been technologies designed to ameliorate ASD, such as cervical disc arthroplasty [2,7–10], identification of the high-risk patients of ASD could better address their value.

The present study aimed to identify the risk factors of second surgery for ASD after ACDF. In order to achieve high rates of follow-up, a long period of observation and a sufficient number of patients were required; thus the study analyzed a national-scaled cohort of ACDF for nearly two decades. To date, this is the first and largest study to address the risk factors of ASD after ACDF, the standard surgery for cervical disc herniation and spondylosis.

2. Experimental section

2.1. Data source and ethical concerns

The study used the National Health Insurance Research Database (NHIRD), a national database containing 26 million administered insurants accumulated from January 1997 to December 2013, provided by the National Health Research Institutes of Taiwan. Due to the unique social-welfare health insurance system operated by the government, it is mandatory for every resident in Taiwan to be enrolled. Thus, the NHIRD has covered 99% of the population since its launch in 1996. The monopolistic national health insurance also offers unrestricted access to any healthcare provider of the patients' choices. The statistics, therefore, gathered by the NHIRD represent a sound cohort for investigation of the natural course and subsequent management of diseases. It is particularly good for studies that need longitudinal observation for repeat treatment (i.e. surgery for ASD) because it allows for the capture of events, even though they may occur in multiple or different institutes and hospitals. The universal coverage and comprehensive follow-up provided a valuable chance to study ASD [11].

All the personal information had already undergone a de-identification and encryption process. Individual and hospital identifiers are unique to the research database and researchers therefore cannot trace individual patients or health service providers. Also, the study was approved by the institutional review board. The whole work was has been reported in line with the STROCSS criteria [12].

2.2. Identification of the study cohort and ACDF surgery

The study included all patients who had been admitted for their first ACDF surgery during the 16-year span, began on January 1st, 1998 till the end of 2013, recorded in the NHIRD. The admission for cervical disc herniation and spondylosis were identified using the ICD9-CM diagnostic codes of 722.0, 722.4 and 722.71, while the surgery of ACDF was confirmed with the procedure codes of 80.51, 81.00 and 81.02 during the same hospitalization.

All identified patients were traced back to the beginning of 1997 (1 year earlier than the start of the cohort) for confirmation of no previous ACDF, laminectomy, or any other cervical spinal surgery. The date of admission was defined as the index date of the ACDF surgery.

All ACDF patients were followed up until the end of 2013 for the second ACDF surgery. To ensure that the second ACDF surgery was not due to short-term complications (e.g. wound dehiscence, infection, pseudarthrosis, or implant dislodgement), any re-operation (i.e. ACDF) within 365 days from the indexed date of the first ACDF were excluded. The study assumed that those patients who had a second ACDF surgery more than one year after the first ACDF were due to ASD, which led to the second ACDF. Theoretically, only severe ASD would be included because less severe ones could have been managed with physical therapies or medical treatment. The model, using a second ACDF as a proxy to identify severe ASD requiring surgery, has also been testified and published for calculation of such incidences of ASD [6]. The true incidence of ASD after ACDF could be higher.

2.3. Identification of risk factors

To identify the risk factors of the second ACDF surgery, the cohort was divided into two groups for comparison: the patients who had only one ACDF and the patients who had two ACDF surgeries during the follow-up. After calculation of all the events of ACDF surgery in the entire cohort, the characteristics were analyzed and compared between the two groups in an attempt to identify potential risk factors of the second ACDF, or reoperation.

All the potential risk factors, including age, sex, and other identifiable risk factors in the cohort were included for subsequent analysis. We adopted the Elixhauser and Charlson Model, in which all the possible comorbidities were classified into 15 subsets (Appendix Table A1). In the cohort, all subjects' co-morbidities were categorized according to Elixhauser's comorbidity model by the presence of either diagnostic codes in the outpatient records or discharge codes in the database within two years before the date of the index date [13,14].

2.4. Statistical methods and analysis

All of the data were linked using the SQL server 2017 (Microsoft Corp, Redmond, WA, USA) and analyzed by Stata 14 (Stata Corp, College Station, TX, USA). Kaplan-Meier method and a log-rank test was used to estimate and compare cumulative re-operation (i.e. second ACDF) rates among different groups. The incidence density method was used to estimate the incidence for the ACDF events.

A competing risk survival regression model with competing-risk of mortality was used to assess risk factors associated with re-operation, the second ACDF. The competing-mortality survival regression model provides accurate estimates of the incidence rates and quantifies effects of covariates in considering the potential occurrence of reoperation impeded by death. Adjusted hazard ratio (aHR) for second ACDF for each factor was estimated by controlling other factors in the model. A two-tailed level of 0.05 was considered statistically significant.

3. Results

3.1. Incidences of second ACDF

During the observation period (1998–2013), a total of 38,149 patients who had the first ACDF were identified in the cohort. During the follow up of 16 years (total 235,185.4 person-years, 6.16 ± 3.91 years), there were 1,092 (2.9%) patients who had a second ACDF, at the mean of 4.66 years (95% C.I. = 4.48–4.85) post- (the first) operation. The incidence rate of the second ACDF was 4.64 per 1,000 person-years (95% C.I. = 4.38–4.93). The cumulative incidence rate of the second ACDF, the estimated incidence rate of ASD, was 7.08% (95% C.I. = 6.42–7.81). (Appendix Fig. A1).

Table 1
Demographic factors and comorbidities by number of ACDF. (1998–2013, n = 38,149).

	One ACDF [a]		Two ACDF [b]		Crude hazard ratio			
	n = 37,057	(%)	n = 1,092	(%)	cHR	(95% C.I.)	P-value	Sig. [c]
Gender								
Female	16,586	(44.8)	447	(40.9)	-ref-			
Male	20,471	(55.2)	645	(59.1)	1.13	(1.00–1.27)	0.048	*
Age at first ACDF								
30-39	4,525	(12.2)	215	(19.7)	3.39	(2.44–4.70)	< 0.001	***
40-49	9,890	(26.7)	391	(35.8)	3.08	(2.24–4.22)	< 0.001	***
50-59	11,191	(30.2)	303	(27.7)	2.44	(1.77–3.36)	< 0.001	***
60-69	7,007	(18.9)	140	(12.8)	1.85	(1.31–2.60)	< 0.001	***
70 and above	4,444	(12.0)	43	(3.9)	-ref-			
Comorbidities								
Depression	1,952	(5.3)	76	(7.0)	1.75	(1.39–2.21)	< 0.001	***
Psychoses	1,335	(3.6)	58	(5.3)	1.95	(1.49–2.54)	< 0.001	***
Diabetes	6,560	(17.7)	145	(13.3)	0.93	(0.78–1.11)	0.442	
Hypertension	11,519	(31.1)	255	(23.4)	0.94	(0.81–1.08)	0.352	
Cerebrovascular disease	3,618	(9.8)	75	(6.9)	0.86	(0.68–1.08)	0.194	
Paralysis	2,044	(5.5)	63	(5.8)	1.17	(0.90–1.50)	0.237	
Other neurological disease	1,143	(3.1)	36	(3.3)	1.34	(0.96–1.87)	0.082	
Congestive heart failure	1,382	(3.7)	24	(2.2)	0.78	(0.53–1.18)	0.247	
Valvular disease	1,583	(4.3)	36	(3.3)	1.00	(0.72–1.40)	0.979	
Chronic pulmonary disease	4,688	(12.7)	127	(11.6)	1.17	(0.97–1.41)	0.095	
Liver disease	4,479	(12.1)	125	(11.4)	1.10	(0.77–1.57)	0.602	
Chronic peptic ulcer disease	1,263	(3.4)	31	(2.8)	1.27	(1.05–1.53)	0.013	*
Peripheral vascular disorder	1,144	(3.1)	24	(2.2)	1.32	(1.01–1.74)	0.045	*
Deficiency anemias	1,913	(5.2)	54	(4.9)	1.06	(0.71–1.59)	0.783	
Collagen vascular diseases	2,125	(5.7)	61	(5.6)	1.23	(0.95–1.59)	0.119	

[a] One ACDF: Patients who had only one ACDF through the whole study period.
[b] Two ACDF: Patients who had at least two ACDF, suggesting second ACDF resulting from ASD.
[c] Significance: *, P < 0.05; **, P < 0.01; ***, P < 0.001.

3.2. Risk factors of ASD and the second ACDF

Age, sex, and psychiatric disorders were the independent risk factors and predictors of ASD, that required a second ACDF. A comparison of risk factors among the patients who had two, the first and second, ACDF and those who had only one ACDF, were conducted. The two groups (i.e. the one- versus the two-ACDF group) had some differences, which suggested that these were the risk factors of ASD, or predictors of a second ACDF. It was demonstrated that patients of male gender, younger age, and a few comorbidities, including depression, psychoses, peptic ulcer, and peripheral vascular disease, were significantly prone to undergo a second ACDF. (Table 1).

After adjustment with the multiple competing risk survival regression model, three independent risk factors for a second ACDF surgery were identified: age, depression, and psychiatric disorders. The younger age of the patient who had a first ACDF had a higher chance of undergoing a second ACDF surgery. The chances of undergoing a second ACDF surgery increased inversely with age (incrementally a 1-to-2-fold higher risk every ten years younger). For example, those patients who were aged 60–69 years had more than a two-fold of risk (aHR = 2.17, 95% CI = 1.53–3.07, p < 0.001) than those older than 70 years. When compared to those over 70 years, patients aged 50–59, 40–49, and 30–39 years had 3, 4, and 4.5 times (aHR = 3.09, 95%CI = 2.21–4.34, aHR = 4.09, 95%CI = 2.91–5.74, and aHR = 4.56, 95%CI = 3.19–6.50, all p < 0.001) greater chance to develop ASD that eventually led to a second ACDF surgery (Table 2).

Furthermore, psychiatric disorders also increased the risk of receiving a second ACDF surgery. Both depression and psychoses led to more than a 40% increased risk of the second ACDF. (Depression, aHR = 1.42, 95% CI = 1.08–1.88, p = 0.013, psychoses, aHR = 1.45, 95% CI = 1.07–1.96, p = 0.016) (Fig. 1).

3.3. Age-specific incidence rates for ASD and the second ACDF surgery

The rates of the second ACDF surgery were significantly different in

Table 2
Adjusted hazard ratio for second ACDF. (1998–2013, n = 38,149).

	Adjusted hazard ratio for second ACDF [a]				
	(aHR)	(95% C.I.)		P-value	Sig. [b]
Gender					
Male vs Female	1.13	(1.00-	1.28)	0.053	
Age at first ACDF					
30–39 v.s. > =70	4.56	(3.19-	6.50)	< 0.001	***
40–49 v.s. > =70	4.09	(2.91-	5.74)	< 0.001	***
50–59 v.s. > =70	3.09	(2.21-	4.34)	< 0.001	***
60–69 v.s. > =70	2.17	(1.53-	3.07)	< 0.001	***
Comorbidities					
Depression	1.42	(1.08-	1.88)	0.013	*
Psychoses	1.45	(1.07-	1.96)	0.016	*
Diabetes	0.95	(0.78-	1.17)	0.650	
Hypertension	1.12	(0.95-	1.32)	0.181	
Cerebrovascular disease	0.88	(0.68-	1.14)	0.338	
Paralysis	1.15	(0.88-	1.49)	0.306	
Other neurological disease	1.18	(0.83-	1.66)	0.361	
Congestive heart failure	0.81	(0.52-	1.24)	0.330	
Valvular disease	0.96	(0.68-	1.36)	0.811	
Chronic pulmonary disease	1.24	(1.01-	1.52)	0.044	
Liver disease	1.08	(0.87-	1.34)	0.482	
Chronic peptic ulcer disease	0.92	(0.63-	1.36)	0.687	
Peripheral vascular disorder	1.05	(0.68-	1.62)	0.816	
Deficiency anemias	1.22	(0.92-	1.63)	0.171	
Collagen vascular diseases	1.11	(0.84-	1.46)	0.451	

[a] A multiple competing risk survival regression model included gender, age and all listed comorbidities as covariates.
[b] Significance: *, P < 0.05; **, P < 0.01; ***, P < 0.001.

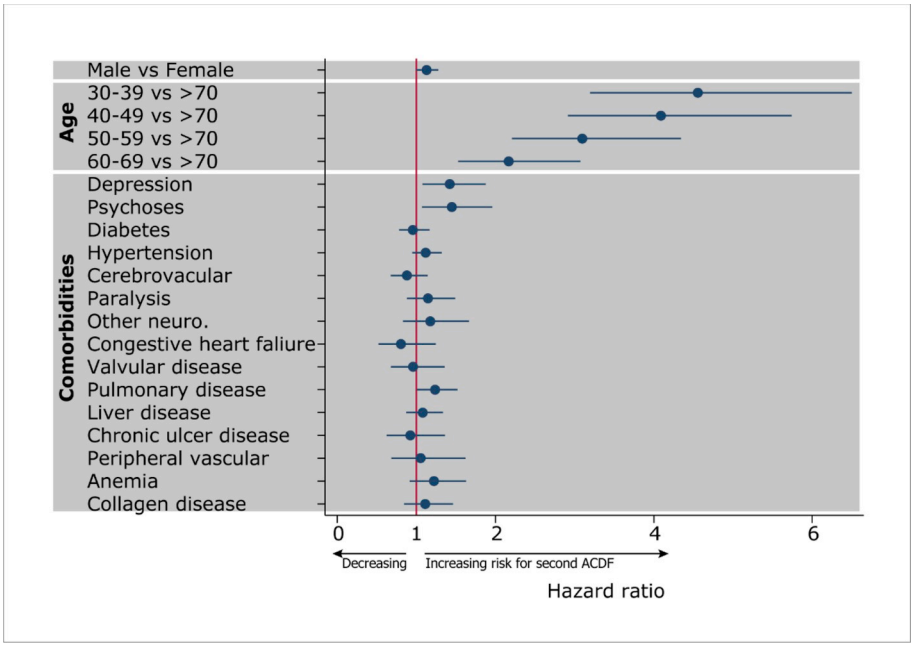

Fig. 1. Adjusted hazard ratios for second ACDF after the first ACDF by potential risk factors. (1998–2013, n = 38,149). A higher adjusted hazard ratio (> 1) suggests higher risk for second ACDF.

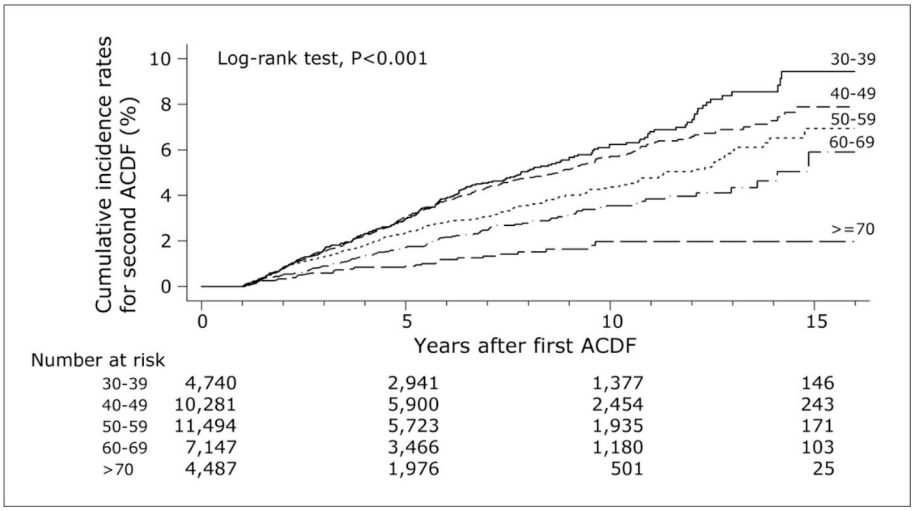

Fig. 2. Kaplan–Meier curve for second ACDF after first ACDF by age groups. (1998–2013, n = 38,149).

each age group, which were compatible with the above demonstrated risk factor of age. Patients who had the first ACDF at younger ages had a higher chance to undergo the second ACDF surgery. For example, patients of the age group 30–39 had the highest incidence rates at 6.28 per 1,000 person-years (5.50–7.18) among all. As the patients got older at the time of the first ACDF, the incidence rates of a second ACDF surgery decreased significantly. For instance, patients aged 40–49, 50–59, 60–69, and over 70 years had different incidences at, respectively, 5.69 (95% CI = 5.16–6.29), 4.49 (4.01–5.03), 3.39 (2.87–4.00), and 1.83 (1.36–2.47) per 1,000 person-years (log-rank test, $p < 0.001$) (Fig. 2).

3.4. Average time to the development of ASD that required a second ACDF

Patients with various risk factors had different time intervals after the first ACDF surgery prior to the second ACDF, or in other words, development of ASD that necessitated another operation. In this cohort, a total of 1,902 patients who underwent the second ACDF surgery were analyzed, and the results demonstrated that the youngest group of patients had the longest time to a second ACDF surgery. For instance, patients aged 30–39 years had an average time of 5.27 years (95% CI = 4.83–5.73), which was 0.76 years longer than others (95% CI = 0.27–1.25, $p < 0.0024$). The other three age groups (40–49, 50–59, 60–69 years) had a similar time interval at 4.66 years (95% CI = 4.48–4.85). However, the patients who were older than 70 years had a significantly shorter time interval at an average of 3.57 years (95% CI = 2.84–4.30) to a second ACDF surgery, which was 1.13 (95% CI = 0.36–1.91) years shorter than all the others ($p = 0.005$) (Fig. 3).

Patients who had psychiatric disorders (i.e. depression and psychoses) also demonstrated a shorter time to the second ACDF surgery. Those patients with depression had 3.37 years (95% CI = 2.95–3.78) before undergoing the second ACDF surgery, which was 1.21 years (95% CI = 0.70–1.72, $p < 0.001$) less than the overall average time. Furthermore, those patients who had psychoses had 3.51 years (95% CI = 3.05–3.98) before undergoing the second surgery, which was 1.39 years (95% CI = 0.24-0.93-1.86) less than the overall mean time to the second ACDF surgery.

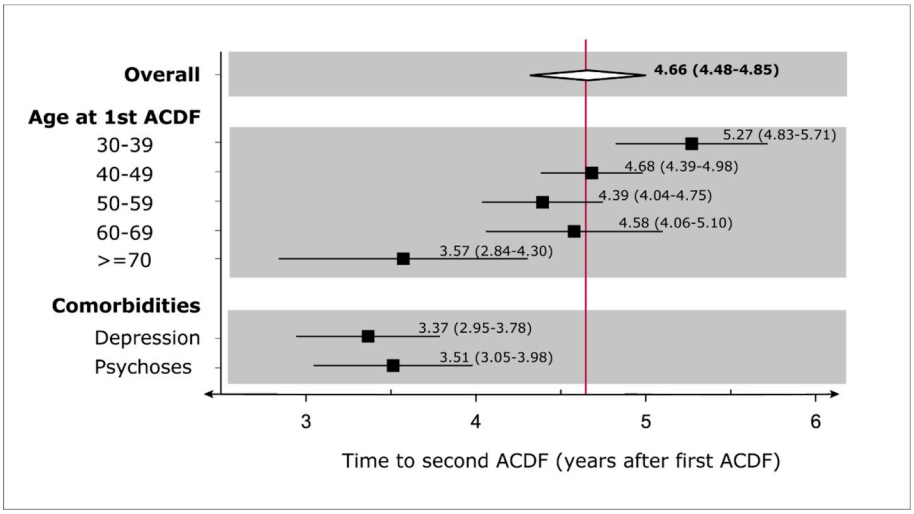

Fig. 3. Average time to second ACDF stratified by risk factors. (1998–2013, n = 1,092).

4. Discussion

This cohort study analyzed a massive number of patients (more than 38,000) who underwent ACDF, a standard surgery for cervical disc herniation or spondylosis. During the follow-up of 16 years, with a comprehensive follow-up rate (almost complete due to the universal coverage of the national health insurance system in the country), the study identified the high-risk groups of patients who developed ASD that required a second ACDF surgery. The second ACDF surgery was considered as the most clinically relevant endpoint of ASD. In this cohort study, predictors of development of ASD were younger age, male gender, and psychiatric disorders (i.e. depression and psychoses) after the first treatment of the discs by ACDF. The model, using the second ACDF surgery to define ASD, has been published before [6]. Since only ASD severe enough that it prompted a second ACDF surgery was counted in the study, the actual incidence of all ASD, including those less or little symptomatic patients, could be higher. Furthermore, the study again validated the findings of a previous study that younger male patients and those who had psychiatric disorders were more likely to develop ASD that required a second ACDF surgery [6].

The results also imply that strategies to minimize the occurrence of ASD development are warranted. In the era of modern spinal surgery, devices aimed at motion preservation rather than arthrodesis, such as an artificial disc, could therefore be advocated [15]. For surgical management of cervical disc herniation and spondylosis, the gold standard of using ACDF could therefore be challenged in high risk patients for ASD if the risk factors could be ascertained. Furthermore, the adaptation of cervical disc arthroplasty (CDA) in the surgical management in the first place could therefore be considered. In fact, many studies have confirmed that in selected patients CDA could be an excellent alternative to ACDF [1–4,8,16–25].

The risk factors and etiologies of ASD have been elusive and are less likely attributed to a single cause, but rather are multifactorial. There was debate about ASD being the natural process of cervical disc degeneration or the consequence of spinal fusion procedures. However, ASD as possibly iatrogenic and accelerated along the natural aging process of cervical spondylosis has been commonly accepted among the spine surgery fraternity [26]. In the literature, many risk factors have been postulated to contribute to ASD. There was a higher incidence rate of ASD after multi-level ACDF than the single-level arthrodesis cases [27]. In the original article, in which ASD was first described after ACDF, the authors claimed risk factors included age, abnormal segmental motion, and pre-existing degeneration [5]. However, the study demonstrated less ASD in multi-level than single-level fusion. Since most of these studies had small numbers of patients who developed ASD with various lengths of follow-up and high rates of loss to follow-up, the results remained controversial.

Many surgeons consider that the incidences of ASD also could be altered by many surgical characteristics. For example, puncture of the annulus for localization purpose [28], the proximity of the anterior cervical plate to the adjacent level [29], and poor post-ACDF global alignment was found to be associated with the development of ASD [30,31]. There were emerging concepts and technologies, such as cervical disc arthroplasty and sagittal parameters, that have claimed effects on ASD [2,3,6,8,24,25]. Nevertheless, most of the existing literature discussed surgery-related factors and none of them was conclusive. In addition, there were conflicting results among these small retrospective studies.

Younger males who received an ACDF surgery were 1.85 times more likely to develop ASD that required a second ACDF surgery compared to older female patients [6]. In that large cohort of 19,385 ACDF patients, repeat ACDF surgery for ASD cumulated steadily in an annual incidence of approximately 0.8%, and younger and male patients were more likely to receive such second operations. Another smaller study, which included nearly 600 patients, demonstrated higher risks of ASD when age at the time of the first ACDF was younger than 50 years [32]. The current study, which was the largest cohort to date, corresponded to previously anticipated results that younger age patients at the first ACDF would have higher risks of development of ASD that prompted the second ACDF surgery. Moreover, in addition to intra-operative factors, investigations of non-surgical factors before the surgery were even more scarce in the literature. Our study was the first to demonstrate the relationship between psychological disorders (depression and psychoses) and the ASD requiring a second ACDF. Although spine surgery is notably related to pain and quality of life, the impact of patients' psychological conditions on spine surgery has remained substantially under-evaluated. The present study suggested an interesting subject worthy of further research.

There were strengths and limitations of the current study. Since the reported incidence rates of ASD were unanimously low among all smaller series, only a large enough cohort with comprehensive follow-up could provide meaningful analysis of the risk factors. The number of patients (38,149) included in the study, with a complete follow-up of 16 years, yielded an accurate censor of the most clinically relevant endpoint of ASD, second ACDF surgery. The model of estimation was tested and published [6], and now adapted for analysis of risk factors. The independent risk factors of ASD—age, sex, and psychiatric disorders—were not only identified, but also quantified. The results also imply that a tailor-made surgical strategy should be considered to ameliorate the chances of development of ASD and subsequent ACDF

surgery.

The limitations of the databased cohort study include the lack of detailed surgical information. The exact approaches, levels, and instruments used for the ACDF surgery were not available for analysis. As a result, we may overestimate the adjacent segment disease requiring surgery as any level that was addressed in second surgery was counted as "adjacent". The effects of surgical complications, including pseudarthrosis, wound infection, and inadequate decompression, were not addressed in the current study. Furthermore, each spine surgeon involved might have various strategies and indications for the second ACDF surgery. For example, ASD could cause various symptoms or signs, such as axial neck pain, instability, spondylotic changes causing myelopathy or radiculopathy. Thus, if the patient presented with a clinical syndrome that did not fit diagnostic criteria, especially when MRIs were not available, ASD with predominantly axial neck pain in the absence of dynamic instability might not need surgery. The surgeons' preferences on timing and options for management of ASD were not well-controlled in the study. Nonetheless, the study provided insights into the development of ASD after spinal fusion surgery.

5. Conclusions

Younger age and experiencing psychiatric disorders are the independent risk factors of ASD requiring a second ACDF surgery. Personalized strategies to ameliorate or postpone the development of ASD are therefore warranted for patients who need ACDF surgery.

Ethical approval

Institutional review board of Taipei Veterans General Hospital (IRB# 2018-09-0006CC).

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Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analyses or interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

Author Contributions

Author Contributions: Conceptualization, W.-C.H., H.-K.C., J.-C.W. and Y.-C.C.; Data curation, Y.-C.C.; Formal analysis, Y.-C.C.; Methodology, Y.-C.C. and J.-C.W.; Project administration, J.-C.W.; Resources, W.-C.H. and, H.-K.C., J.-C.W. and Y.-C.C.; Writing—review and editing, J.-C.W. and Y.-C.C.

Trial registry number

The study had been registered in ClinicalTrials.gov (UIN = NCT03826329).

Full detail can be accessed via https://clinicaltrials.gov/show/NCT03826329.

Guarantor

Yu-Chun Chen.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.06.002.

Appendix

Table A1
ICD-9-CM Coding Algorithms for Comorbidities

Comorbidities	ICD-9-CM codes
Depression	300.4, 301.12, 309.0, 309.1, 311
Psychoses	295.x-298.x, 299.1
Diabetes	(uncomplicated) 490x-492.x, 493.x, 494x-505.x, 506.4 (complicated) 250.0–250.3, 648.0
Hypertension	(uncomplicated) 401.1, 401.9, 642.0 (complicated) 401.0, 402.x-405.x, 642.1, 642.2, 642.7, 642.9
Cerebrovascular disease	362.34, 430.x-438.x
Paralysis	342.x-344.x, 438.2–438.5
Other neurological disorders	330.x-331.x. 332.0, 333.4, 333.5, 334.x, 335.x, 340, 341.1–341.9, 345.x, 347.x, 780.3, 784.3
Congestive heart failure	398.91, 402.01, 402.91, 404.01, 404.11, 404.13, 404.93, 428.x, 402.11, 404.03, 404.91
Valvular disease	093.2, 394.x-397.1, 397.9, 424.x, 746.3–746.6, V42.2, V43.3
Chronic pulmonary disease	490x-492.x, 493.x, 494x-505.x, 506.4
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 456.0, 456.1, 456.20, 571.0, 571.2–571.9, 572.3, 572.8, V42.7

(*continued on next page*)

Table A1 (*continued*)

Comorbidities	ICD-9-CM codes
Peptic ulcer disease excluding bleeding	531.41, 531.51, 531.61, 531.7, 531.91, 532.41, 532.51, 532.61, 532.7, 532.91, 533.41, 533.51, 533.61, 533.7, 533.91, 534.41, 534.51, 534.61, 534.7, 534.91
Peripheral vascular disorders	440.x, 441.x, 442.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4
Deficiency anemia	280.1–281.9, 285.2, 285.9
Rheumatoid arthritis/collagen vascular diseases	701.0, 710.x, 714.x, 720.x, 725.x

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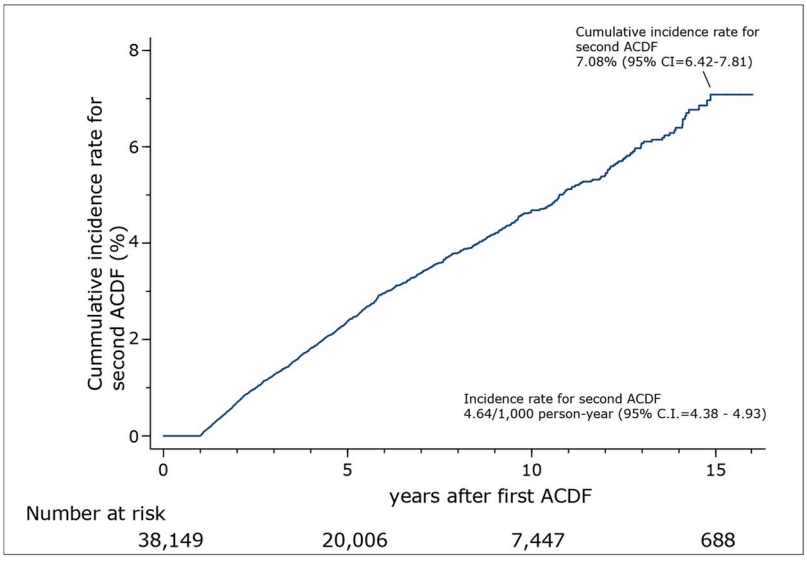

Fig. A1. Cumulative incidence for second ACDF. (1998–2013, n = 38,149).

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