POMORSKI UNIWERSYTET MEDYCZNY W SZCZECINIE

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Wyniki leczenia dyslokacji w obrębie złącza kręgowo-podstawnego przy użyciu stabilizacji przeznasadowej

Outcomes of transpedicular fixation in craniovertebral dislocation

Rozprawa doktorska w dziedzinie nauk medycznych i nauk o zdrowiu

Dyscyplina nauki medyczne

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Spis treści

1. Wykaz publikacji będących przedmiotem rozprawy doktorskiej

Cele pracy zostały zrealizowane poprzez cykl pięciu spójnych tematycznie artykułów naukowych opublikowanych w latach 2020-2022, w tym trzech pełnych metaanaliz (publikacje 1, 3 i 4) oraz dwóch pełnych prac oryginalnych (publikacje 2 i 5). Cykl zatytułowany jest ‘Wyniki leczenia dyslokacji w obrębie złącza kręgowo-podstawnego przy użyciu stabilizacji przeznasadowej’.

1. Klepinowski T, Pala B, Cembik J, Sagan L (2020) **Prevalence of high-riding vertebral artery: a meta-analysis of the anatomical variant affecting choice of craniocervical fusion method and its outcome**. World Neurosurg. 143:e474–e481; https://doi.org/10.1016/j.wneu.2020.07.182
   Impact Factor = 2,104; Punktacja Ministerstwa Edukacji i Nauki = 70 pkt

2. Klepinowski T, Żyłka N, Pala B, Poncyljusz W, Sagan L (2021) **Prevalence of high-riding vertebral arteries and narrow C2 pedicles among Central-European population: a computed tomography-based study**. Neurosurg Rev. 44(6):3277-3282; https://doi.org/10.1007/s10143-021-01493-6
   Impact Factor = 2,800; Punktacja Ministerstwa Edukacji i Nauki = 100 pkt

3. Klepinowski T, Cembik J, Sagan L (2020) **Risk of the high-riding variant of vertebral arteries at C2 is increased over twofold in rheumatoid arthritis: a meta-analysis**. Neurosurg Rev. 44(4):2041–2046; https://doi.org/10.1007/s10143-020-01425-w
   Impact Factor = 2,800; Punktacja Ministerstwa Edukacji i Nauki = 100 pkt

4. Klepinowski, T, Limanówka, B & Sagan, L (2021) **Management of post-traumatic craniovertebral junction dislocation: A PRISMA-compliant systematic review and meta-analysis of case reports**. Neurosurg Rev. 44(3):1391–1400; https://doi.org/10.1007/s10143-020-01366-4
   Impact Factor = 2,800; Punktacja Ministerstwa Edukacji i Nauki = 100 pkt

5. Klepinowski T, Sagan L (2022) **EQ-5D health-related quality of life questionnaire in craniovertebral instability treated with posterior fixation with or without occipital plating: a comparative study with matched datasets**. J Craniovert Jun Spine 2022;13(1):72-9. https://doi.org/10.4103/jcvjs.jcvjs_125_21
   Punktacja Ministerstwa Edukacji i Nauki = 70 pkt

Sumaryczny współczynnik Impact Factor wymienionych publikacji: 10,504

Sumaryczna punktacja Ministerstwa Edukacji i Nauki wymienionych publikacji: 440 pkt

2. Stosowane skróty

95% CI – 95% confidence interval (95% przedział ufności)

AAD – atlantoaxial dislocation (dyslokacja szczytowo-obrotowa)

AOD – atlantooccipital dislocation (dyslokacja szczytowo-potyliczna)

AQUA – Anatomical Quality Assessment

ASIA – American Spinal Cord Injury

BAI – basion-axial interval (odcinek basion-obrotnik)

BDI – basion-dens interval (odcinek basion-ząb)

C2InH – C2 internal height (wysokość wewnętrzna kręgu C2)

C2IsH – C2 isthmus height (wysokość cieśni kręgu C2)

C2P – C2 pedicle (nasada kręgu C2)

CCI – craniocervical instability (niestabilność złącza kręgowo-podstawnego)

CCJ – craniocervical junction (złącze kręgowo-podstawne)

CT – computed tomography (tomografia komputerowa)

CVJ – craniovertebral junction (złącze kręgowo-podstawne)

EQ-5D – EuroQol-5 Dimensions

EQ-5D-3L – 3-level version of EuroQol-5 Dimensions (3-poziomowa wersja EuroQol-5 Dimensions)

HRQoL – health-related quality of life (jakość życia związana ze zdrowiem)

HRVA – high-riding vertebral artery (wysoko biegnąca tętnica kręgowa)

IQR – interquartile range (przedział międzykwartylowy)

mJOA – modified Japanese Orthopaedic Association

MOOSE - Meta-analyses of Observational Studies

NDI – Neck Disability Index

NP – narrow pedicle of C2 (wąska nasada kręgu C2)

NOS – Newcastle-Ottawa scale (skala Newcastle-Ottawa)

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RA – rheumatoid arthritis (reumatoidalne zapalenie stawów)

rCCI – revised C1-condyle interval (zrewidowany odcinek C1-kłykieć)

RR – relative risk / risk ratio (ryzyko względne)

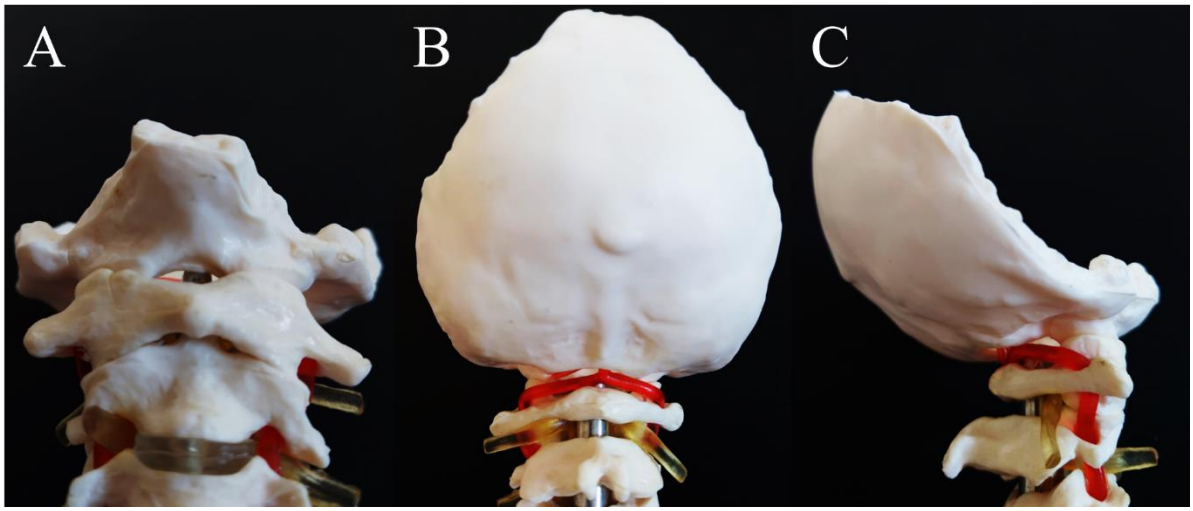
SD – standard deviation (odchylenie standardowe)

VA – vertebral artery (tętnica kręgowa)

3. Wstęp

Złącze kręgowo-podstawne traktowane jest jako biomechaniczna całość składająca się z kręgu obrotowego, kręgu szczytowego oraz powierzchni podstawnej kości potylicznej wraz z kłykciami potylicznymi, które razem tworzą następujące stawy: parzysty szczytowo-potyliczny i nieparzysty, bo potrójny, szczytowo-obrotowy[1] (Rycina 1). Staw szczytowo-potyliczny uważany jest za najstabilniejszy ze stawów dzięki mocującemu go aparatowi więzadłowemu, zaś staw szczytowo-obrotowy za obdarzony największą ruchomością[1,2]. Ruchomość tego drugiego sprawia jednak, że jest on dużo bardziej podatny na niestabilność[1]. Dlatego też zdecydowana większość niestabilności złącza kręgowo-podstawnego wynika z zaburzeń w obrębie stawu szczytowo-obrotowego, nie zaś szczytowo-potylicznego[1,3,4]. Pojęcia dyslokacji i niestabilności w odniesieniu do złącza kręgowo-podstawnego w literaturze anglosaskiej stosowane są zamiennie[5].

Niestabilność w obrębie złącza kręgowo-podstawnego jest zjawiskiem wysoce niebezpiecznym. Ze względu na sąsiedztwo krytycznych struktur naczyniowo-nerwowych może się wiązać z groźnym krwotokiem, nagłym zatrzymaniem krążenia lub ciężkimi ubytkami neurologicznymi. Jedną z tych istotnych struktur jest tętnica kręgowa (VA), a ściślej jej końcowy odcinek V2, cały odcinek V3 oraz początkowy odcinek V4. Uszkodzenie VA może wiązać się z niedokrwieniem w obrębie rdzenia przedłużonego i móżdżku, co niesie ryzyko poważnych zaburzeń neurologicznych, takich jaki zespół boczny opuszki (zespół Wallenberga)[6], zespół podopuszkowy Opalskiego[7], zespół Babińskiego-Nageotte'a[8], zespół Reinholda (ang. *hemimedullary Reinhold's syndrome*)[8],

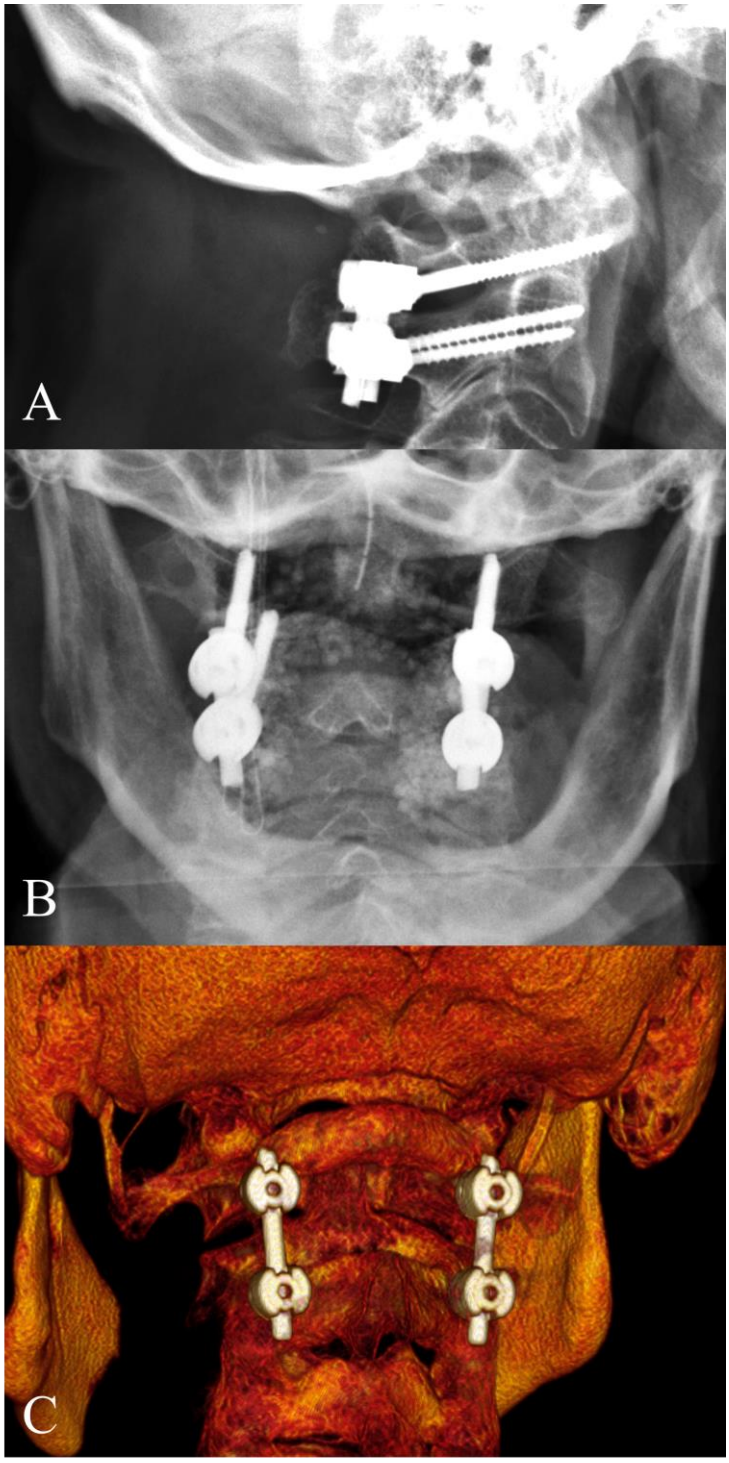


Rycina 1 *Model przedstawiający złącze kręgowo-podstawne. A - widok z przodu. B - widok z tyłu. C - widok z boku od strony prawej. Źródło własne.*

czy zespół Cestan-Chenais[9]. Uszkodzenie okolicy złącza opuszkowo-rdzeniowego może prowadzić bezpośrednio do zgonu w wyniku przerwania włókien z ośrodków pneumotaksycznego i apneustycznego. W innych przypadkach może dojść do niedowładów czterokończynowych, porażenia rotacyjnego (gdy osłabienie siły mięśniowej postępuje w kolejności: tożstronna kończyna górna, tożstronna kończyna dolna, przeciwstronna kończyna dolna, przeciwstronna kończyna górna) lub porażenia krzyżowego Bella (ang. *Bell's cruciate paralysis;* gdy uszkodzenie w obrębie styku szyjno-opuszkowego prowadzi do porażenia siły mięśniowej w kończynach górnych ze względnym nienaruszeniem siły mięśniowej kończyn dolnych)[10,11]. Część przypadków przebiega skąpoobjawowo lub zupełnie bez objawów. Niemniej jednak i w tych sytuacjach niestabilność może wymagać zaopatrzenia, gdyż istnieje niebezpieczeństwo dekompensacji z nagłym uciskiem struktur naczyniowo-nerwowych i pojawieniem się nieodwracalnych deficytów neurologicznych. Spośród przyczyn niestabilności złącza kręgowo-podstawnego należy wymienić urazy (między innymi wypadki komunikacyjne, upadki, pobicia), guzy nowotworowe niszczące więzadła i torebki stawowe w obrębie złącza, choroby reumatologiczne takie jak reumatoidalne zapalenie stawów lub łuszczycowe zapalenie stawów, choroby infekcyjne (zespół Grisela), czy wrodzone malformacje w obrębie złącza (os odontoideum).

Leczenie niestabilności złącza kręgowo-podstawnego może być zachowawcze lub operacyjne. Na leczenie zachowawcze składa się korzystanie z kołnierza ortopedycznego lub ortezy czaszkowej (na przykład typu Halo) z ewentualnym stosowaniem wyciągu. Aktualne trendy światowe wskazują na korzyści płynące z wczesnej stabilizacji wewnętrznej pozwalającej na szybkie uruchamianie i rehabilitację pacjenta[12,13]. Opcje leczenia operacyjnego na przestrzeni lat zmieniały się kilkukrotnie. Aktualnie dominującą metodą jest stabilizacja Goela-Harmsa przez masy boczne C1 i przez nasady C2 (Rycina 2). Przybliżone kąty trajektorii śrub przez masy boczne kręgu C1 to 17° przyśrodkowo i 22° dogłowowo, natomiast dla śrub przez nasady C2 to 20-30° przyśrodkowo i 25° dogłowowo[14]. Termin stabilizacja przeznasadowa (ang. *transpedicular fixation*) przyjął się w naukowej literaturze anglosaskiej w odniesieniu do stawu szczytowo-obrotowego, choć teoretycznie nie odzwierciedla on w pełni przebiegu wkręcanych śrub, gdyż anatomicznie kręg C1 nie posiada nasad[15–17]. Łuk przedni i tylny kręgu szczytowego połączone są częściami bocznymi, zwanymi również masami bocznymi. W trakcie stabilizacji przeznasadowej szczytowo-obrotowej śruby w kręg C1

wprowadza się więc przez jego masy boczne. Z kolei w kręgu C2 śruby prowadzone są przez nasady jego łuku i tutaj określenie ‘przeznasadowe’ jest w pełni zasadne.



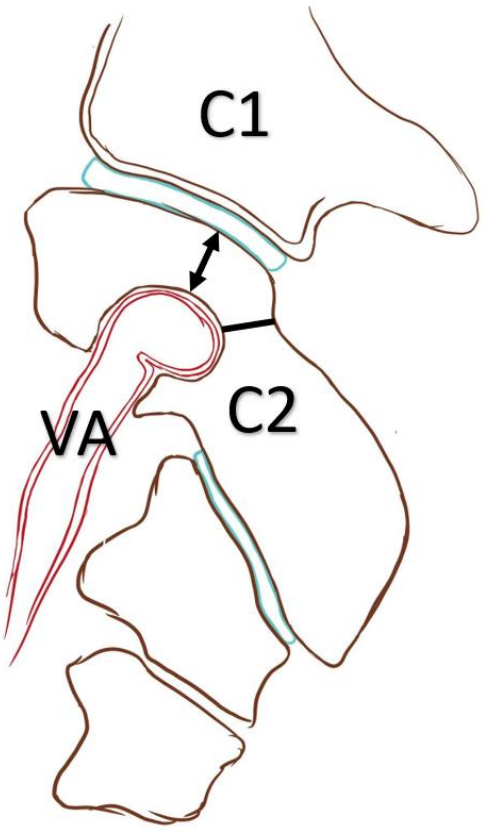
Rycina 2 *Zdjęcie RTG w projekcji bocznej (A), przednio-tylnej z otwartymi ustami (B) oraz rekonstrukcja trójwymiarowa tomografii komputerowej (C) ukazujące stan po stabilizacji szczytowo-obrotowej metodą Goela-Harmsa. Źródło własne.*

Wyniki leczenia niestabilności w obrębie złącza kręgowo-podstawnego stabilizacją przez nasady C2 można rozpatrywać w aspektach klinicznym (stan neurologiczny, jakość życia związana ze zdrowiem) i radiologicznym (położenie śrub w stosunku do VA na co wpływa obecność wariantów VA), które mimo rozróżnienia są integralnie ze sobą związane. Podziału można też dokonać na podstawie czasu oceny wyników: wczesne (bezpośrednio w okresie okołooperacyjnym, w trakcie hospitalizacji) i odległe (na wizycie kontrolnej).

Bardzo istotnym aspektem stabilizacji złącza kręgowo-podstawnego jest prowadzenie elementów konstrukcji stabilizującej w bezpośredniej bliskości tętnic kręgowych, stąd kluczowe jest zachowanie ich w stanie nienaruszonym, bez jatrogennego ich uszkodzenia. Wprowadzenie śruby do otworu wyrostka poprzecznego kręgu C2, w którym biegnie tętnica kręgowa, wiąże się z ryzykiem dramatycznego pogorszenia stanu klinicznego pacjenta, śródoperacyjnej dekompensacji hemodynamicznej i możliwych ciężkich powikłań neurologicznych, gdyż tętnica ta zaopatruje w krew między innymi struktury tylnej jamy czaszki – rdzeń przedłużony i móżdżek. Tym bardziej jest to groźne, jeśli dojdzie do uszkodzenia po stronie dominującej lub jedynej prawidłowo rozwiniętej tętnicy kręgowej w przypadku jednostronnej hipoplazji lub aplazji tego naczynia[18]. Ryzyko naruszenia jego ciągłości jest istotnie wyższe w sytuacji wariantu anatomicznego zwanego wysoko biegnącą tętnicą kręgową (HRVA)[19]. Do czynienia z tym wariantem mamy w przypadku, gdy wysokość cieśni kręgu C2 wynosi ≤ 5 mm i/lub wysokość wewnętrzna od otworu wyrostka poprzecznego do powierzchni stawowej górnej C2 wynosi ≤ 2 mm mierzone na przekroju strzałkowym zrekonstruowanym 3 mm do boku od bocznej granicy kanału kręgowego[20] (Rycina 3). Dotychczas częstość występowania tego wariantu pozostawała przedmiotem kontrowersji, ze znacznymi rozbieżnościami w literaturze światowej[20–39]. Istnieją też pojedyncze doniesienia, że reumatoidalne zapalenie stawów (RA) może być czynnikiem ryzyka dla nabytej postaci HRVA, co może być o tyle istotne, że jednym z powikłań RA bywa objęcie procesem zapalnym stawu C1-C2 i jego niestabilność wymagająca instrumentacji przeznasadowej[40]. W literaturze do tej pory brakowało jednak metaanalizy, która w sposób systematyczny zebrałaby dostępne dane i poddała statystycznej analizie, wyznaczając globalną i regionalną częstość występowania HRVA wraz z 95% przedziałami ufności (95% CI). Brakowało również opracowania wyznaczającego ryzyko względne (RR) wystąpienia HRVA dla osób z RA w porównaniu do osób bez RA. Przeprowadzenie takich metaanaliz ze wszystkich

dostępnych danych dostarczy istotnych epidemiologicznie informacji, zwiększy świadomość dotyczącą złożoności przedoperacyjnego planowania operacji złącza kręgowo-podstawnego, ukaże rzeczywistą skalę ryzyka i przyczyni się do poprawy bezpieczeństwa śródoperacyjnego polepszając bezpośrednie (wczesne) wyniki stabilizacji przeznasadowej. Metaanalizy te mogą też posłużyć do zaproponowania algorytmu postępowania klinicznego w przypadku obecności HRVA po stronie dominującej lub niedominującej.

W literaturze można dostrzec również deficyt informacji z zakresu postępowania i wyników w leczeniu pourazowej niestabilności złącza kręgowo-podstawnego. Może to wynikać z faktu, że szczytowo-potyliczne i szczytowo-obrotowe przemieszczenia po urazie cechują się wysoką śmiertelnością[41]. Aktualnie w dobie znacznego postępu resuscytacji przedszpitalnej coraz więcej chorych przeżywa do czasu wykonania badań obrazowych i kwalifikacji do zabiegu neurochirurgicznego. Zidentyfikowana luka informacyjna w medycznej literaturze w zakresie wyników leczenie podgrupy pourazowej jest tym bardziej istotna, iż zaczęły pojawiać się doniesienia o braku konieczności włączania kości potylicznej do stabilizacji, a nawet jego szkodliwości[42]. Dlatego uzasadnionym wydaje się przeprowadzenie przeglądu systematycznego z



Rycina 3 *Zobrazowanie parametrów wykorzystywanych do zdefiniowania wysoko biegnącej tętnicy kręgowej. Przekrój strzałkowy przez staw szczytowo-obrotowy w punkcie 3 mm dobocznie od bocznego brzegu kanału kręgowego. VA - tętnica kręgowa. Linia z dwoma grotami - wysokość wewnętrzna. Linia - wysokość cieśni. C1 – kręg szczytowy. C2 – kręg obrotowy. Źródło własne.*

metaanalizą dostępnych przypadków klinicznych pacjentów z pourazowym przemieszczeniem w obrębie złącza szyjno-potylicznego. Metaanaliza przypadków klinicznych, choć obarczona większym ryzykiem błędu systematycznego (ang. *risk of bias*), to jest jedynym rozwiązaniem dla schorzeń rzadkich, które dokładnie raportowane w literaturze są jedynie w małych seriach i częstokroć mają zero przypadków w jednym z dwóch ramion badania (tj. w próbie badanej lub kontrolnej). Co więcej, jak pokazują badania z 2018 roku przeprowadzone przez Sampayo-Cordero i współpracowników, odpowiednio przeprowadzona metaanaliza przypadków klinicznych w tychże rzadkich jednostkach cechuje się stosunkowo dużą dokładnością i zgodnością w porównaniu z metaanalizami większych badań klinicznych[43].

Odległe wyniki natomiast w dużej mierze są związane z jakością życia pacjentów. Aktualnie bardzo niewiele jest danych w literaturze na temat jakości życia związanej ze zdrowiem (HRQoL) chorych po stabilizacji złącza kręgowo-podstawnego z dostępu tylnego. Szeroko stosowanym kwestionariuszem do oceny HRQoL w chirurgii kręgosłupa jest EuroQol-5 Dimensions (EQ-5D), który ocenia pięć domen: (1) zdolność poruszania się, (2) samoobsługa, (3) zwykłe czynności, (4) ból / dyskomfort, (5) niepokój / przygnębienie. Wynik zapisany w postaci pięciocyfrowego kodu jest łatwy do przekształcenia w wymierny parametr - użyteczność, która zasadniczo przyjmuje wartości od +1 (idealna jakość) do 0 (śmierć), choć stosowane są również wartości ujemne (do –0,523) rozumiane jako jakość zdrowia gorsza niż śmierć[44]. EQ-5D ocenia także na skali wizualnej ogólną jakość życia związaną ze zdrowiem od 0 (najgorszy wyobrażalny stan zdrowia) do 100 (najlepszy wyobrażalny stan zdrowia). Z uwagi na fakt, iż aktualnie w literaturze kwestionowana jest konieczność dołączania potylicy do stabilizacji[45], postanowiono dodatkowo zbadać wpływ tego elementu na HRQoL.

4. Cele

Cele *ogólne* pracy były następujące:

(1) Określenie globalnej i regionalnej częstości występowania HRVA jako wariantu anatomicznego wpływającego na wczesne wyniki leczenia niestabilności złącza kręgowo-podstawnego z wykorzystaniem śrub przeznasadowych – Publikacja 1.
(2) W przypadku niewielkiej liczby europejskich badań z tego zakresu również wyznaczenie częstości HRVA w populacji polskiej – Publikacja 2.
(3) Oszacowanie ryzyka względnego (RR) wystąpienia HRVA u osób z reumatoidalnym zapaleniem stawów – Publikacja 3.
(4) Ocena wyników neurologicznych leczenia pourazowej niestabilności w obrębie złącza kręgowo-podstawnego przy użyciu stabilizacji przez nasady C2 wraz z określeniem wpływu dołączenia kości potylicznej do fuzji na te wyniki – Publikacja 4.
(5) Określenie HRQoL przed stabilizacją oraz na wizycie kontrolnej wraz z identyfikacją istotnych korelatów i predyktorów HRQoL – Publikacja 5.
(6) Ocena wpływu dołączenia kości potylicznej do stabilizacji na HRQoL – Publikacja 5.

Cele *szczegółowe* wraz z hipotezami zerowymi i pełną metodologią zostały omówione w każdej załączonej publikacji osobno.

Projekt pracy doktorskiej został zatwierdzony przez właściwą Komisję Bioetyczną bez konieczności opiniowania (KB-0012/24/04/2020/Z).

5. Omówienie wyników

5.1 Publikacja 1

Prevalence of high-riding vertebral artery: a meta-analysis of the anatomical variant affecting choice of craniocervical fusion method and its outcome

Przeszukano bazy danych PubMed MEDLINE, Web of Science, EMBASE, SciELO, a także China National Knowledge Infrastructure wykorzystując przetłumaczoną frazę ‘wysoko biegnąca tętnica kręgowa’ i odpowiednie synonimy. Kryteria włączenia i wyłączenia zostały dokładnie omówione w sekcji metodologicznej załączonej publikacji. Spośród pierwotnie wyszukanych 681 publikacji, ostatecznie do oceny jakościowej, jak i ilościowej włączonych zostało 20 prac naukowych opublikowanych na przestrzeni lat 1997-2019. 16 z nich pochodziło z Azji, 2 z Ameryki Północnej oraz 2 z Europy[20–39]. Nie zidentyfikowano żadnych badań na populacjach afrykańskiej i australijskiej. Metaanaliza w modelu efektów losowych objęła 3126 osób i 7496 stron. Aby zapewnić usystematyzowaną strukturę metaanalizy zastosowano się do rekomendacji o nazwie Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Ocena ryzyka błędu systematycznego przy pomocy narzędzia Anatomical Quality Assessment (AQUA) wykazała, że największe ryzyko dotyczyło metodologii zakwalifikowanych prac (12 z 20 było wysokiego ryzyka), zaś najmniejsze ryzyko było związane z projektem badań (19 spośród 20 było niskiego ryzyka). Dominującą modalnością oceny wysokości cieśni kręgu C2 była tomografia komputera – 18 spośród 20 włączonych do metaanalizy prac. W dwóch badaniach autorzy identyfikowali wysoko biegnącą tętnicę kręgową (HRVA) na preparatach kadawerowych. Globalna częstość występowania HRVA została wyliczona na 20,9% (95% CI 16,5 – 25,8; I^2 = 87,5%; Q Cochrana = 111,6; p < 0,001) wśród osób bez reumatoidalnego zapalenia stawów (RA), natomiast uwzględniając łącznie osoby bez RA, jak i z RA częstość ta wyniosła 25,3% (95% CI 19,6 – 31,5; I^2 = 92,3%; p < 0,001). Częstość u osób z RA oszacowano na 42,9% (95% CI 23,8 – 63,1; I^2 = 64,68%; Q Cochrana = 8,49; p = 0,037). U kobiet HRVA występowała istotnie częściej (26,82%) niż u mężczyzn (15,20%; p = 0,0016). Nie wykryto różnic między stroną lewą czy prawą (50,8% versus 49,2%; p = 1,0). Największa częstość HRVA została zaobserwowana w populacji europejskiej – 23,93% (95% CI 20,49 – 27,55; I^2 = 0,0%; p = 0,80), następnie azjatyckiej – 21,48% (95% CI 15,96 – 27,56; I^2 = 88,3%; p < 0,001) i północnoamerykańskiej – 19,17% (95% CI 2,76 – 43,20; I^2 = 94,1; p < 0,001). Różnice te jednak nie osiągnęły istotności statystycznej (p = 0,20; test jednorodności chi-kwadrat).

Celem zmniejszenia ryzyka śródoperacyjnego uszkodzenia tętnicy kręgowej, a przez to poprawy wyników leczenia stabilizacją przeznasadową doktorant w publikacji zaproponował praktyczny algorytm dotyczący postępowania klinicznego u chorych z HRVA, który szerzej omówiony został w sekcji 6.1. Jest to w literaturze pierwsza próba usystematyzowania postępowania klinicznego u pacjentów z HRVA kwalifikowanych do stabilizacji złącza kręgowo-podstawnego.

5.2 Publikacja 2

Prevalence of high-riding vertebral arteries and narrow C2 pedicles among Central-European population: a computed tomography-based study

383 kolejne skany tomografii komputerowej kręgosłupa szyjnego (766 potencjalnych punktów wprowadzenia śrub w nasady C2) ocenione zostały przez dwoje niezależnych badaczy. Pomiarów nie wykonywano u osób po operacjach w obrębie złącza kręgowo-podstawnego, ze złamaniami kręgu C2, o nieodpowiedniej jakości technicznej wykonania (w tym artefakty wynikłe z poruszenia się w trakcie akwizycji), u osób poniżej 18 roku życia oraz u chorych na reumatoidalne zapalenie stawów. Wśród analizowanych osób było 237 kobiet (61,9%) i 146 mężczyzn (38,1%). Średni wiek badanych wyniósł 43,2 lata (przedział 22 – 86 lat). Wykazano, że w populacji polskiej (jako reprezentatywnej dla Europy Środkowej) częstość występowania co najmniej jednej HRVA wynosi 25,3% (95% CI 21,1– 29,8), co się przekłada na 16,7% (95% CI 14,2–19,4) potencjalnych punktów wprowadzenia śrub. Z kolei częstość występowania co najmniej jednej wąskiej nasady C2 (NP) wyliczono na 36,8% (95% CI 32,1–41,7) badanych oraz 23,8% (95% CI 20,8–26,8) z potencjalnych miejsc wprowadzenia śrub. Wśród osób z obustronnymi HRVA dokonano pomiarów grubości łuków C2, aby ocenić możliwość zastosowania śrub przez blaszki łuków kręgowych (ang. *translaminar screws*) doktorant dokonał pomiarów grubości tych blaszek na przekrojach poprzecznych tomografii komputerowych. Średnia grubość blaszek łuku u tych badanych (z obustronnymi HRVA) wyniosła 5,48 mm (odchylenie standardowe [SD] = 1,21 mm) po stronie lewej i 5,33 mm (SD = 0,97 mm) po prawej, przy czym wąskie łuki (grubość poniżej 4 mm) stwierdzono zaledwie u 13,3% po lewej i 10% po prawej potwierdzając tym samym, że w większości przypadków nawet obustronnych HRVA śruby przez blaszki łuków pozostają istotną alternatywą. Analogicznie, w przypadku obustronnych wąskich nasad C2, blaszki łuków tych kręgów zwykle pozostają odpowiednio szerokie (5,49 mm [SD = 1,06 mm] i 5,45 mm [SD = 0,83 mm] odpowiednio dla stron lewej i prawej), zaś wąskie blaszki łuków

(poniżej 4 mm) stwierdzono jedynie u 7,3% osób po lewej i 2,4% po prawej osób z obustronnymi NP, co sugeruje, że śruby przez blaszki łuków stanowić mogą opcję ratunkową w przypadku niemożności wprowadzenia śrub przeznasadowych. Kappy Cohena jako miary zgodności między dwoma obserwatorami wyniosły: $\kappa_1 = 0{,}848$ dla lewej HRVA (zgodność znakomita według przyjętej skali opisanej w metodologii opublikowanego artykułu – ang. *excellent*), $\kappa_2 = 0{,}873$ dla prawej HRVA (znakomita), $\kappa_3 = 0{,}784$ dla lewej NP (dobra – ang. *good*), $\kappa_4 = 0{,}795$ dla prawej NP (dobra). Zgodności wewnątrz jednego obserwatora po czasie od dwóch do trzech miesięcy wyniosły: $\kappa_5 = 0{,}852$, $\kappa_6 = 0{,}834$, $\kappa_7 = 0{,}864$, $\kappa_8 = 0{,}912$ odpowiednio dla lewej HRVA, prawej HRVA, lewej NP i prawej NP (znakomite). Zgodności między dwoma różnymi programami komputerowymi Syn.govia i OsiriX wyniosły $\kappa_9 = 0{,}940$, $\kappa_{10} = 0{,}703$, $\kappa_{11} = 0{,}896$, $\kappa_{12} = 0{,}774$ odpowiednio dla lewej HRVA (znakomita), prawej HRVA (dobra), lewej NP (znakomita) i prawej NP (dobra).

5.3 Publikacja 3

Risk of the high-riding variant of vertebral arteries at C2 is increased over twofold in rheumatoid arthritis: a meta-analysis

W sposób systematyczny przeszukano najważniejsze bazy danych: PubMed MEDLINE, Web of Science, EMBASE, SciELO oraz China National Knowledge Infrastructure stosując odpowiednie tłumaczenia i synonimy terminów ‘wysoko biegnąca tętnica kręgowa’ i ‘reumatoidalne zapalenie stawów’. Spośród 346 pierwotnie zidentyfikowanych badań, finalnie na podstawie ustalonych kryteriów włączenia i wyłączenia, szczegółowo opisanych w sekcji ‘Metody’ omawianej publikacji, do syntezy jakościowej włączono pięć opublikowanych w latach 2005 – 2018 artykułów[23,25,29,34,46], natomiast do metaanalizy zakwalifikowano cztery z nich[23,25,29,34,46]. Jedno badanie (Miyata i współautorzy[40]), które włączono do jakościowego przeglądu systematycznego zostało, mimo spełnienia kryteriów włączenia, wykluczone z analizy ilościowej ze względu na nieakceptowalnie wysokie ryzyko błędu systematycznego wynikające z odmiennej, nieuznawanej definicji HRVA i znacznie odbiegającej od średniej częstości występowania HRVA. Aby zapewnić usystematyzowaną strukturę metaanalizy zastosowano listę kontrolną o nazwie Meta-analyses of Observational Studies (MOOSE), która zawiera sześć domen i 35 istotnych punktów do uwzględnienia w metaanalizach badań obserwacyjnych. Wszystkie cztery prace zakwalifikowane do ilościowej syntezy były autorstwa naukowców z Azji. Jakość włączonych do metaanalizy badań została

oceniona przy pomocy skali Newcastle-Ottawa i wykazała, że w domenach ‘selekcja’ oraz ‘wynik’ wszystkie artykuły miały umiarkowane ryzyko błędu systematycznego, zaś w domenie ‘porównywalność’ większość prac obarczona była wysokim ryzykiem takiego błędu. W sumie do metaanalizy włączono 308 uczestników, których podzielono na dwie grupy. Do grupy A z ekspozycją (osoby chorujące na reumatoidalne zapalenie stawów) włączono 125 badanych, natomiast do grupy B bez ekspozycji na badany czynnik (osoby nieobciążone reumatoidalnym zapaleniem stawów) zakwalifikowano 183 osoby. Średni wiek w obu grupach był porównywalny (62,1 lat w grupie A versus 59,9 lat w grupie B). Po przeprowadzeniu statystycznych obliczeń metaanalizy z wykorzystaniem oprogramowania MetaXL 5.3, EpiGear International Pty Ltd. (Brisbane, Australia) w modelu efektów stałych wykazano, że ryzyko względne (RR) wystąpienia wysoko biegnącej tętnicy kręgowej w populacji z reumatoidalnym zapaleniem stawów jest około dwukrotnie większe niż u osób bez tej choroby – RR = 2,11 (95% CI 1,47 – 3,05; I^2 = 15,19%, Q Cochrana = 3,54, p = 0,32). Test całkowitej istotności metaanalizy dla RR wykazał $p < 0,001$.

5.4 Publikacja 4

Management of post-traumatic craniovertebral junction dislocation: A PRISMA-compliant systematic review and meta-analysis of case reports

Po przeszukaniu baz danych PubMed MEDLINE i Web of Science, do badania włączono 46 artykułów naukowych z lat 2015 – 2020 obejmujących łącznie 141 przypadków klinicznych pourazowej niestabilności w obrębie złącza kręgowo-podstawnego, u których wdrożono leczenie zanim nastąpił ewentualny zgon[16,47–90]. Dla usystematyzowania struktury przeprowadzonego badania zastosowano wytyczne oraz listę kontrolną PRISMA. W grupie było 90 mężczyzn (63,8%), 46 kobiet (32,6%), a płeć pięciu osób pozostała nieznana. Średni wiek pacjentów wyniósł 39,2 lat. Okres obserwacji po zastosowanym leczeniu średnio objął 15,4 miesięcy (przedział 0,5 – 60 miesięcy). W mechanizmie urazów dominowały wypadki komunikacyjne (70,9%) oraz upadki (24,6%). Najczęstszym podtypem pourazowej niestabilności w obrębie złącza była dyslokacja szczytowo-obrotowa (AAD; 62,4%). Rzadziej obserwowano dyslokację szczytowo-potyliczną (AOD; 27,7%) i podtyp mieszany (9,9%). Leczenie operacyjne stabilizacją z dostępu tylnego stosowane było w zdecydowanej większości przypadków (95,7%), przy czym poziomami zwykle włączanymi do fuzji były C1-C2 (45,2%), O-C2 (19,3%), O-C3 (13,3%) i O-C4 (8,1%). Dla przypadków AOD najczęściej wybieranymi

segmentami były O-C2 (35,9%), które również dominowały w podtypach mieszanych (57,1%). 4,3% pacjentów leczonych było zachowawczo, przy czym wszyscy ci mieli AAD, a żaden AOD (bez istotności statystycznej, p = 0,129). 27,2% badanych było bez deficytów neurologicznych przed i po operacji. Spośród 100 osób (76,3%), które miały ubytki neurologiczne przed operacją, 59% (n = 59) odniosło poprawę stanu neurologicznego, 37% (n = 37) było stabilnych, zaś 4% (n = 4) uległo pogorszeniu. Nasilony ból okolicy podpotylicznej i karku był obecny u 43 chorych (30,5%), natomiast w obserwacji na wizycie kontrolnej uległ znaczącej poprawie u 83,7% z nich. 70 pacjentów (49,6%) miało włączoną kość potyliczną do stabilizacji. Wśród chorych z objawami neurologicznymi przy prezentacji, brak instrumentacji kości potylicznej wiązał się istotnie z częstszą poprawą neurologiczną (48,1% versus 33,3%) i mniejszym odsetkiem neurologicznej stagnacji (9,3% versus 41,7%; p = 0,0013; test chi-kwadrat). Model regresji wielorakiej wykazał, że predyktorem stanu neurologicznego na wizycie kontrolnej w tej populacji może być fakt dołączenia kości potylicznej do fuzji (β = -0,30; p = 0,023), zaś nie są to podtyp niestabilności (szczytowo potyliczna versus szczytowo-obrotowa; β = 0,12; p = 0,307), płeć (β = 0,19; p = 0,120), ani wiek (β = -0,08; p = 0,514). Pełen zrost kostny uzyskano u 93,8% pacjentów.

5.5 Publikacja 5

EQ-5D health-related quality of life questionnaire in craniovertebral instability treated with posterior fixation with or without occipital plating: a comparative study with matched datasets

Do badania włączono 60 chorych, u których przeprowadzono stabilizację złącza kręgowo-podstawnego przy użyciu śrub wprowadzanych między innymi w nasady C2. W próbie znalazło się 30 kobiet i 30 mężczyzn. Średni wiek badanych określono na 37,2 lat. Mediana obserwacji wyniosła 26,3 miesięcy z przedziałem międzykwartylowym (IQR) od 10,8 do 47,3. Mediana przedoperacyjnej jakości życia związanej ze zdrowiem (HRQoL) ocenionej w kwestionariuszu EQ-5D wyniosła 0,254 (IQR -0,025 do 0,504). Na wizycie kontrolnej bezpośredniej lub telefonicznej medianę HRQoL oszacowano na 0,779 (IQR 0,387 do 0,864). Wzrost był istotny statystycznie (p < 0,001). Mediana wzrostu HRQoL wyniosła 0,508 (IQR 0,128 do 0,717). Pomimo poprawy, jakość ta w dalszym ciągu była niższa niż dolny kwartyl (25. centyl) populacji polskiej dopasowanej pod względem wieku (0,894). Przed operacją domeną jakości zdrowia najgorzej ocenianą był ból / dyskomfort, a także niepokój / depresja – 94,4% chorych w każdej z tych domen

deklarowało problemy umiarkowane lub krańcowe. Wymiarem HRQoL najmniej dotkniętym przed operacją była samoobsługa – 30,6% ankietowanych nie było w stanie się umyć lub ubrać, 50% miało z tym umiarkowane problemy, zaś 19,4% nie miało z tym jakichkolwiek trudności. Na wizycie kontrolnej w dalszym ciągu ból i dyskomfort dominowały, jako przysparzające pacjentom najwięcej problemów – 51,6% odczuwało umiarkowane dolegliwości, a 9,7% krańcowy ból lub dyskomfort. Na wizycie kontrolnej najwięcej ankietowanych doceniło brak problemów w poruszaniu się (61,3%). 35 pacjentów (58,3%) miało dołączoną kość potyliczną (C0) do stabilizacji. Mediany HRQoL przedoperacyjnie w grupie bez dołączonej kości potylicznej to 0,100. W grupie z C0 zaś mediana wyniosła 0,310 (różnica nieistotna statystycznie, p = 0,069). Pooperacyjne mediany HRQoL w grupie z dołączoną C0 i bez wyniosły odpowiednio 0,670 i 0,810 (p = 0,061). Mediany wzrostów HRQoL w tych grupach to odpowiednio 0,540 i 0,400 (p = 0,692), co wskazuje na podobne wyniki w obu grupach i możliwość braku wpływu dołączenia kości potylicznej do konstruktu stabilizującego na HRQoL. Model wielorakiej regresji liniowej wykazał, że predyktorami HRQoL w dalszej obserwacji na wizycie kontrolnej mogą być wiek (β = -0,004; p = 0,049) oraz długość okresu hospitalizacji liczona w dniach (β = -0,134; p = 0,010). Inne czynniki nie uzyskały istotności statystycznej. Spośród klasycznych pomiarów radiologicznych dotyczących niestabilności złącza kręgowo-podstawnego tylko przedoperacyjny parametr odległości zęba obrotnika od linii Wackenheima korelował z HRQoL (rho Spearmana = -0,432; p = 0,028). Bliski osiągnięcia istotności statystycznej w korelacji z HRQoL był współczynnik Powersa (rho Spearmana = -0,416; p = 0,054 dla pomiaru przedoperacyjnego oraz rho = -0,418; p = 0,121 dla pomiaru pooperacyjnego).

6. Dyskusja

6.1 Publikacja 1

Prevalence of high-riding vertebral artery: a meta-analysis of the anatomical variant affecting choice of craniocervical fusion method and its outcome

Dotychczas w literaturze przedstawiane były znaczne rozbieżności w częstościach występowania HRVA – od 8,3% do ~40%[30,91]. Przeprowadzona metaanaliza w modelu efektów losowych ukazała jednak, że 95% CI tego wariantu anatomicznego wynosi od 16,5% do 25,8%, znacznie zawężając poprzedni przedział. Dane te ukazują powszechność HRVA i podkreślają jak istotne jest przedoperacyjne planowanie oraz świadomość obecności HRVA w przypadku stabilizacji z wykorzystaniem śrub przez nasady C2 lub śrub przez staw C1/C2, gdyż w obu tych technikach HRVA znacznie zwiększa ryzyko uszkodzenia VA[92]. Wyjaśnienie przyczyny, dla której wąska cieśń zwiększa te ryzyko również w przypadku śrub przeznasadowych leży w anatomicznie ścisłych stosunkach cieśni i nasady kręgu C2, co wykazał Naderi i jego współpracownicy w 2004 roku proponując wspólną nazwę 'komponent nasadowo-cieśniowy' (ang. *pediculo-isthmic component*)[93].

Jedna praca obejmująca populację czeską sugerowała znaczną przewagę występowania HRVA po stronie lewej (17,8% versus 12,1%; p = 0,011). Wykonana przez doktoranta metaanaliza, uwzględniająca dziewięć spośród zakwalifikowanych prac, wykazała jednak, że stosunek strony lewej do prawej jest podobny (lewa: 50,8% [95% CI 33,8 – 67,6]; prawa: 49,2% [95% CI 32,4 – 66,2]; p ~ 1,0; test U Manna-Whitneya).

W ramach dyskusji doktorant zaproponował algorytm postępowania w sytuacjach, gdy na etapie planowania przedoperacyjnego stwierdzona zostanie HRVA po stronie dominującej lub niedominującej VA. W przypadku jednostronnej HRVA i tożstronnie dominującej VA zalecono, by odstąpić od śruby przezstawowej, zaś śruba przeznasadowa jest dopuszczalna przy zachowaniu najwyższej ostrożności i zastosowaniu systemu nawigacyjnego. Należy również rozważyć przeprowadzenie śruby przez blaszki łuków, czyli translaminarnie. Podobne zalecenia zostały zaproponowane w przypadku obustronnych HRVA. Z kolei, jeśli mamy do czynienia z jednostronną HRVA i tożstronnie niedominującą bądź hipoplastyczną VA, wówczas nie zaleca się śrub przezstawowych, natomiast śruby przeznasadowe po obu stronach są dopuszczalne i wykonalne bez dużego ryzyka powikłań. Gdy po obu stronach nie występuje HRVA, to zarówno technika przezstawowa, jak i przeznasadowa są akceptowalne, a wybór zależy

od preferencji operatora. Zidentyfikowana niewielka ilość badań na temat HRVA w populacji europejskiej posłużyła za inspirację do zbadania omawianego wariantu anatomicznego tętnicy kręgowego w próbie reprezentatywnej dla tej populacji i opracowania kolejnej publikacji (oznaczonej jako Publikacja 2). Z kolei odkryta możliwa zależność między reumatoidalnym zapaleniem stawów a HRVA stanowiła kamień węgielny pod metaanalizę mającą na celu oszacowanie RR dla HRVA u pacjentów z RA (Publikacja 3).

6.2 Publikacja 2

Prevalence of high-riding vertebral arteries and narrow C2 pedicles among Central-European population: a computed tomography-based study

W populacji polskiej jako reprezentatywnej dla Europy Środkowej, średnia częstość występowania HRVA wyniosła 25,3% (95% CI 21,1 – 29,8) i mieści się w 95% przedziale ufności dla wyznaczonej częstości w skali globalnej[94]. Częstość występowania przynajmniej jednej NP u pacjenta w kontekście globalnym nie została dotychczas oszacowana, niemniej jednak uzyskana w tym badaniu (36,8% [95% CI 32,1 – 41,7]) jest wyższa niż w doniesieniu Yeoma i współpracowników[38] z 2013 roku dotyczącego populacji koreańskiej (23,8%). Wyjaśnieniem tych rozbieżności mogą być znane różnice w budowie kręgosłupa szyjnego w zależności od pochodzenia etnicznego[95]. Dla przykładu, stwierdzono, iż anatomicznie najmniejsza szerokość nasad kręgu C4 występuje u kobiet populacji europejskiej i amerykańskiej (średnio 4,1 mm), zaś największa szerokość nasad kręgu C7 obecna może być u mężczyzn populacji azjatyckiej (średnio 7,7 mm)[95]. Podobnie sytuacja kształtować może się w chorobach dotykających kręgosłup szyjny: kostnienie więzadła podłużnego tylnego znacznie częściej występuje u Azjatów – 4,8% (95% CI 2,8 – 8,1) niż u rasy kaukaskiej – 1,3% (95% CI 0,7 – 2,3) z poziomem istotności statystycznej $p = 0,005$ [96].

Z uwagi na istniejące różnice rasowe w anatomii i fakt, iż przeprowadzona wcześniej metaanaliza (publikacja 1) naświetliła ograniczoną ilość badań europejskich (jedynie dwie prace[21,97], z których waga jednej w wykresie drzewkowym znacznie przewyższyła wagę drugiej), doktorant wraz ze współautorami postanowił w ramach dyskusji wykonać uzupełniającą metaanalizę wyłącznie podgrupy badań europejskich z uwzględnieniem wyników badania z populacją polską (publikacja 2). Spośród trzech badań[21,97,98] zawierających sumarycznie 944 uczestników, uaktualniona częstość występowania przynajmniej jednej wysoko biegnącej tętnicy kręgowej w Europie wyniosła 24,52%

(95% CI 21,83 – 27,32, I^2 = 0,0 [0 – 32,7], Q Cochrana = 0,31; model efektów losowych) i jest wyższa niż stwierdzona poprzednio (23,93% [95% CI 20,49 – 27,55]. Dodanie niniejszej publikacji pozwoliło także na zawężenie przedziału ufności i równiejsze rozłożenie wag analizowanych prac, zmniejszając tym samym ryzyko błędu systematycznego wynikającego z małej ilości dostępnych danych (ang. *data availability bias*).

Co więcej, po raz pierwszy zostały wyznaczone parametry morfometryczne kręgu C2 (wysokość cieśni, szerokość nasad, szerokość blaszek łuków) w populacji polskiej. Te dane mogą być wykorzystane w przedoperacyjnym planowaniu stabilizacji złącza kręgowo-podstawnego u polskich pacjentów. Wówczas, w przypadku zidentyfikowania wąskich nasad C2 lub wysoko biegnącej tętnicy kręgowej, można z wyprzedzeniem zaplanować dodatkowe śródoperacyjne kroki zmniejszające ryzyko uszkodzenia tętnicy kręgowej, takie jak stabilizacja przez blaszki łuku lub zastosowanie ultrasonografii dopplerowskiej, jak zasugerował Lofrese [99].

6.3 Publikacja 3

Risk of the high-riding variant of vertebral arteries at C2 is increased over twofold in rheumatoid arthritis: a meta-analysis

Pomimo istniejących przesłanek, że reumatoidalne zapalenie stawów może zwiększać ryzyko obecności HRVA[40], brakowało ilościowego podsumowania dostępnych danych. Na cztery włączone do przeglądu i metaanalizy badania[23,25,29,34], trzy sugerowały podniesione ryzyko, jedna zaś wskazywała, że takie ryzyko mogłoby być nawet zmniejszone. Przeprowadzona przez doktoranta metaanaliza wykazała, że RR = 2,11 (95% CI 1,47 – 3,05, I^2 = 15,19%, Q Cochrana = 3,54, model efektów stałych), co dowodzi, że ryzyko – na podstawie aktualnie dostępnych danych – może być podniesione ponad dwukrotnie. Przypuszczalnym wytłumaczeniem częstszego występowania HRVA w RA jest postępująca degradacja gęstości mineralnej kości w wyniku toczącego się przewlekłego procesu zapalnego z udziałem interleukiny-6 i czynnika martwicy guza w obrębie stawów szczytowo-obrotowych, które są w bezpośrednim sąsiedztwie cieśni kręgu C2[100,101]. Tętniąca tętnica kręgowa regularnie uderzająca w osłabioną zapalnie i osteoporotycznie kość stopniowo doprowadza do jej ścieńczenia, co w efekcie zmniejsza wysokość cieśni. Wprowadzenie śruby przeznasadowej przez taką chorobowo zmienioną kość wiąże się z ryzykiem zarówno uszkodzenia tętnicy kręgowej, jak i obluzowania implantu w dalszej perspektywie.

Poznanie zależności między wysoko biegnącą tętnicą kręgową a reumatoidalnym zapaleniem stawów jest dla tej podgrupy szczególnie istotne z tego względu, iż pacjenci ci są częściej narażeni niż populacja ogólna na wystąpienie niestabilności w obrębie złącza kręgowo-postawnego[102]. Jak tłumaczy Gillick i współpracownicy, niestabilność ta w przypadku RA jest wynikiem przewlekłego procesu zapalnego z proliferacją tkanki łącznej włóknistej i naczyniowej z następową formacją łuszczki wokół stawów szczytowo-obrotowych bocznych i przedniego (między zębem C2 a łukiem przednim C1)[103]. Tworząca się zapalna łuszczka doprowadza do poluzowania torebki stawowej i więzadeł z możliwym podwichnięciem w stawach szczytowo-obrotowych lub atraumatycznym patologicznym złamaniem zęba obrotnika. Górny odcinek kręgosłupa szyjnego w RA jest istotnie zajęty nawet w 65% przypadków[102]. Wobec tego, pacjenci z RA częściej będą wymagać operacji stabilizującej złącze kręgowo-podstawne z wykorzystaniem śrub przeznasadowych. Kontinuum tych zjawisk doprowadza do sytuacji, w której podgrupa z podniesionym prawdopodobieństwem niestabilności i wymogu stabilizacji, ma również największe ryzyko jatrogennego uszkodzenia VA w wyniku występowania HRVA, co może znacznie pogorszyć ich wyniki leczenia. Świadomość ponad dwukrotnie częstszej obecności wysoko biegnącej tętnicy kręgowej u pacjentów z reumatoidalnym zapaleniem stawów i przygotowanie opcji alternatywnych, takich jak chociażby śruby przez blaszki łuku, może z kolei przyczynić się do poprawy tych wyników.

6.4 Publikacja 4

Management of post-traumatic craniovertebral junction dislocation: A PRISMA-compliant systematic review and meta-analysis of case reports

W tym przeglądzie systematycznym z metaanalizą przypadków klinicznych podjęto próbę nawiązania dyskusji na bardzo istotny aspekt stabilizacji złącza kręgowo-podstawnego. Jak uzasadnia Atul Goel, większość niestabilności w obrębie złącza jest wynikiem nieprawidłowości stawu szczytowo-obrotowego, nie zaś szczytowo-potylicznego i nie wymaga stabilizacji odcinka C0-C1[45]. Przewaga niestabilności szczytowo-obrotowej znalazła potwierdzenie również w podgrupie pourazowej (62,4%)[104]. Niemniej jednak, co zaprezentowano w publikacji 4, nierzadko i wśród tych chorych z niestabilnością wyłącznie szczytowo-obrotową dołącza się potylicę do stabilizacji (18,2%). Jak wykazano, może to spowalniać postęp rehabilitacji w wyniku czego na wizycie kontrolnej wyniki leczenia mogą być gorsze niż gdyby górny biegun

konstruktu stabilizacyjnego zakończyć na poziomie C1-C2, bez dołączania potylicy. W praktyce klinicznej dobrymi markerami pomocnymi w odróżnieniu AOD od AAD są radiologiczne pomiary takie jak odcinek basion-ząb (BDI), odcinek basion-obrotnik (BAI), a w szczególności zrewidowany odcinek C1-kłykieć (rCCI), dla którego punkt odcięcia 2,5 mm ma wysoką czułość i swoistość w odniesieniu do AOD[105].

Wykonana metaanaliza wykazała również, że najczęściej wykonywanym rodzajem stabilizacji w podgrupie pourazowej jest metoda Goela-Harmsa ze śrubami prowadzonymi przez masy boczne C1 i nasady C2 (75,5%). Z innych metod rzadziej wykorzystywanych należy wspomnieć o metodach Brooksa czy Sonntaga-Dickmana, gdzie stosowany jest tak zwany ‘wiring’, czyli poprowadzenie drutów podtrzymujących łuki kręgów C1 i C2 – technika stosowana głównie w populacji pediatrycznej. Inną stosowaną czasem metodą są prowadzone przez blaszki łuków śruby translaminarne, które miało 12,4% chorych leczonych operacyjnie w przeprowadzonym przeglądzie. Metoda ta została wprowadzona w 2004 roku przez Wrighta[106] i współpracowników. Warunkiem do zastosowania śrub translaminarnych jest grubość łuku ponad 3,5 mm mierzone na przekroju osiowym tomografii komputerowej. Technika ta zapewnia mniejszą wytrzymałość konstruktu stabilizującego niż śruby przeznasadowe[107], jednak jest bezpieczniejsza i może być wykorzystana w przypadku wąskich nasad (NP) lub wysoko biegnącej tętnicy kręgowej (HRVA).

W przeglądzie autorzy zwrócili również uwagę na częsty brak spójnego sposobu raportowania wyników leczenia w literaturze. Opisy symptomatologii często są podawane w sposób nieilościowy, utrudniający analityczną syntezę danych. Niekonsekwentnie stosowane są różnego rodzaju skale do wyrażenia symptomatologii takie jak mJOA, ASIA, Nurick, Neck Disability Index lub często żadna z nich. Niewątpliwie ustalenie konsensusu w tym zakresie przyczyniłoby się do zwiększenia jakości metaanalizy.

6.5 Publikacja 5

EQ-5D health-related quality of life questionnaire in craniovertebral instability treated with posterior fixation with or without occipital plating: a comparative study with matched datasets

W literaturze można odnaleźć kwantyfikację HRQoL z użyciem kwestionariusza EQ-5D dla wielu schorzeń kręgosłupa[108–113]. W przypadku zaburzeń balansu strzałkowego i osiowego kręgosłupa szyjnego o typie kifoskoliozy u dorosłych wyliczono średni współczynnik EQ-5D równy 0,511 (SD = 0,224), co było wynikiem poniżej 25. centyla populacji dopasowanej wiekiem i płcią[108]. Podobnie jak w publikacji nr 5, domeną najbardziej obniżającą jakość życia był ból i dyskomfort. Lepszą HRQoL niż w niestabilności złącza kręgowo-podstawnego wytłumaczyć można typowo bardziej przewlekłym charakterem deformacji, do których chory jest w stanie się stopniowo zaadaptować. Z kolei w ostrych złamaniach trzonów kręgów HRQoL jest już dużo niższa (0,270 [95% CI 0,220 – 0,310])[109] i bardziej zbliżona do tej w CCI przed operacją (0,254 [IQR -0,025 do 0,504]). Co więcej, podobnie jak w złamaniach trzonów, po skutecznym leczeniu CCI HRQoL ulega znacznej poprawie podczas wizyty kontrolnej: 0,690 (95% CI 0,660 – 0,720) versus 0,779 (IQR = 0,387 do 0,864)[109]. Różnice w zastosowanych miarach rozkładu wynikają z odmiennych rozkładów danych w poszczególnych pracach (normalny versus brak rozkładu normalnego).

Model wielorakiej regresji liniowej obejmujący cztery zmienne niezależne i jedną zmienną zależną wykazał, że istotnymi predyktorami jakości życia związanej ze zdrowiem na wizycie kontrolnej są wiek oraz długość hospitalizacji. Im starszy pacjent i im dłużej przebywa on w szpitalu, tym gorszą ma przewidywaną HRQoL. Podeszły wiek pociąga za sobą choroby towarzyszące, w tym występowanie zespołu kruchości, mniejsze zdolności do rehabilitacji i mniejsze rezerwy na powrót do zdrowia. Z kolei wpływ przedłużonej hospitalizacji na HRQoL można tłumaczyć obecnością powikłań, pobytem w oddziale intensywnej terapii, czy też zaburzonym gojeniem się rany. Co warte podkreślenia, w modelu wielorakiej regresji liniowej nie uzyskano istotności statystycznej w odniesieniu do dołączenia kości potylicznej do stabilizacji, co w kontekście danych uzyskanych z publikacji nr 4 oraz 5 może ukazywać brak bezpośredniego przełożenia stanu neurologicznego na HRQoL lub może wynikać z homogenności populacji w publikacji nr 4 (grupa pourazowa) i heterogenności populacji w publikacji nr 5.

W omawianej publikacji wykazano, iż stosunek linii Wackenheima do wierzchołka zęba obrotnika, może korelować z przedoperacyjną jakością życia związaną ze zdrowiem (rho = -0,432, p = 0,028). W przypadku gdy wierzchołek zęba C2 znajdował się brzusznie lub stycznie do tej linii, obserwowano wyższą HRQoL wyrażoną współczynnikiem EQ-5D. Niemniej jednak wynik ten należy interpretować ostrożnie, gdyż na odległość zęba od linii Wackenheima wpływ mieć może celowo przybrana pozycja kręgosłupa szyjnego, w której wykonywane jest badanie radiologiczne[114]. Co więcej, mimo stwierdzonej korelacji liniowej, przeprowadzona przez doktoranta analiza wielorakiej regresji liniowej nie potwierdziła tego parametru jako niezależnego predyktora przedoperacyjnej HRQoL.

6.6 Związek poszczególnych publikacji z tytułem rozprawy doktorskiej

Opublikowane prace naukowe są powiązane tematycznie, koncentrują się wokół wyników leczenia dyslokacji złącza kręgowo-podstawnego z wykorzystaniem stabilizacji przez nasady obrotnika, a jednocześnie mają zróżnicowany, wielowymiarowy charakter. Publikacje numer 1, 2 i 3 są wyrazem dążenia do poprawy okołooperacyjnych wyników leczenia dzięki zmniejszeniu ryzyka uszkodzenia tętnicy kręgowej w obrębie otworu wyrostka poprzecznego obrotnika podczas wprowadzania śrub metodą przeznasadową w kręg C2. Celem zmniejszenia tego ryzyka i dla poprawy wyników leczenia stabilizacją przeznasadową doktorant zaproponował praktyczny algorytm dotyczący postępowania klinicznego u chorych z HRVA. Publikacja 4 przedstawia zarówno postępowanie jak i wyniki leczenia homogennie wyselekcjonowanej populacji z wyłącznie pourazową niestabilnością złącza kręgowo-podstawnego i ocenia dodatkowe czynniki (w tym dołączenie kości potylicznej do konstrukcji stabilizującej) kształtujące wynik leczenia oceniany na wizycie kontrolnej. Publikacja 5 charakteryzuje jakość życia związaną ze zdrowiem przed i po stabilizacji złącza kręgowo-podstawnego przy wykorzystaniu śrub wprowadzanych w nasady C2. HRQoL jest jednym z istotniejszych wyników leczenia z perspektywy pacjenta, gdyż odzwierciedla wpływ zdrowia bezpośrednio na codzienne funkcjonowanie, w tym na zdolność poruszania się, samoobsługę (mycie, ubieranie się), pracę, aktywności w czasie wolnym, dolegliwości bólowe lub nastrój.

6.7 Implikacje kliniczne

Wyniki uzyskane z przeprowadzonych badań mogą znaleźć zastosowanie w praktyce klinicznej. Zaproponowane w publikacji nr 1 rekomendacje postępowania u chorych z HRVA w zależności od strony dominującej VA mogą pozwolić na wybór bezpieczniejszej techniki operacyjnej, poprawiając bezpośrednie okołooperacyjne wyniki

leczenia. Sugerowane jest, aby pomiary radiologiczne cieśni i nasad C2 były standardem w przedoperacyjnym planowaniu, jako że – co udowodniono w publikacji nr 2 - cechują się wysoką zgodnością między różnymi obserwatorami i wewnątrz jednego obserwatora niezależnie od stosowanego oprogramowania in silico. Jest to szczególnie istotne u chorych z reumatoidalnym zapaleniem stawów, którzy przyjmowani są z podwichnięciem w stawie szczytowo-obrotowym lub z inwaginacją zęba obrotnika do otworu wielkiego, i którzy mają planowany zabieg stabilizacji złącza kręgowo-podstawnego z dostępu tylnego. Mają oni bowiem średnio ponad dwukrotnie wyższe ryzyko obecności HRVA, a co się z tym wiąże również wyższe ryzyko jatrogennego uszkodzenia tętnicy kręgowej. Kolejną ważną implikacją kliniczną jest wniosek z publikacji nr 4, iż u chorych z pourazową niestabilnością wyłącznie szczytowo-obrotową (C1-C2) włączenie potylicy do stabilizacji może nieść negatywne skutki w postaci gorszej rehabilitacji i opóźnionej poprawy neurologicznej. Kluczowe dla rozróżnienia czystej AAD od AOD lub łączonej AAD z AOD wydają się być pomiary radiologiczne, w szczególności parametry BDI, BAI i rCCI. Z publikacji nr 5, w ocenie doktoranta, najistotniejsze do codziennej praktyki są statystycznie istotne predyktory: wiek i długość hospitalizacji. Proponując elektywną stabilizację złącza kręgowo-podstawnego pacjentom w podeszłym wieku i z dużym ryzykiem powikłań okołooperacyjnych przedłużających pobyt w szpitalu, świadomość tych predyktorów pozwoli na przekazanie choremu kolejnej istotnej informacji potrzebnej do świadomej zgody na zabieg. Dzięki temu pacjent będzie miał realne oczekiwania w odniesieniu do spodziewanej jakości życia związanej ze zdrowiem. Dodatkowo, istotna jest wiedza, że na przedoperacyjną HRQoL najbardziej negatywnie wpływa odczuwany ból i dyskomfort, zaś HRQoL na wizycie kontrolnej obniżają głównie problemy z wykonywaniem zwykłych czynności, takich jak nauka, praca czy aktywności w czasie wolnym. Pozwoli to na korzystniejszą alokację zasobów oddziałowych (większy nacisk na leczenie przeciwbólowe w okresie okołooperacyjnym) i poszpitalnych (pomoc psychologiczna i środowiskowa).

6.8 Ograniczenia

Cykl prac, mimo iż porusza wiele aspektów dotyczących wyników leczenia - związane z tętnicą kręgową, wyniki radiologiczne, jakość życia, stan neurologiczny - niestabilności w obrębie złącza kręgowo-podstawnego, to nie jest wolny od niedoskonałości. Ograniczeniem publikacji nr 1 był niewątpliwie fakt, że większość badań pochodziła z Azji. Jedynie dwie prace wywodziły się z Ameryki Północnej i dwie z Europy. Żaden

artykuł nie obejmował populacji afrykańskiej ani australijskiej. Te ograniczenie zostało częściowo zaadresowane w publikacji nr 4, gdzie autorzy wyznaczyli częstość HRVA wśród próby składającej się z 383 Polaków jako grupy reprezentatywnej dla populacji Europy Środkowej. Było to pierwsze takie badanie obejmujące populację polską. Dzięki temu następnie została przedstawiona uaktualniona zbiorcza częstość występowania HRVA w Europie z bardziej równomiernym rozkładem wag w wykresie drzewkowym. Dodatkowo, większość z prac była obarczona wysokim ryzykiem błędu systematycznego w kwestii metodologii. W związku z tym, że w publikacji nr 2 zgodność pomiarów nasad C2 między obserwatorami i między programami komputerowymi oceniona została jedynie jako 'dobra' (kappa 0,61 do 0,80), pomiary między poszczególnymi badaczami i uzyskiwane różnymi programami mogą się nieco różnić. W publikacji nr 3 największym mankamentem była niewielka liczba badań spełniających kryteria włączenia. Zaledwie cztery prace zostały objęte analizą, wśród których znalazło się 308 osób (125 w grupie A i 183 w grupie B). Niemniej jednak wystarczyło to, aby uzyskać istotność statystyczną wyznaczonego współczynnika ryzyka względnego (RR = 2,11 [95% CI 1,47-3,05], I^2 = 15,19%, Q Cochrana = 3,54). Głównym ograniczeniem publikacji nr 4 był rodzaj prac, na których oparto metaanalizę. Opisy przypadków i ich serie stanowią najniższy poziom dowodu naukowego. Metaanaliza na ich podstawie została wykonana dlatego, iż pourazowa niestabilność złącza kręgowo-podstawnego jest zjawiskiem na tyle rzadkim, że większość badaczy raportuje ją jedynie w niewielkich grupach lub łącznie z innymi przyczynami bez analizy w podgrupach. To sprawia, że defragmentacja danych z całej próby do podgrupy pourazowej jest często niemożliwa, a więc badanie takie nie może być włączone do metaanalizy. Innym ograniczeniem tej publikacji był przedział lat, z których prace były akceptowane, co znacznie zredukowało liczbę włączonych prac oraz pacjentów. Wybrano okres jedynie ostatnich pięciu lat ze względu na postępy w resuscytacji przedszpitalnej, diagnostyce obrazowej i technikach operacyjnych. To pozwoliło na zwiększenie homogenności zakwalifikowanych przypadków kosztem ich mniejszej liczby. W publikacji nr 5 użyto tylko jednego narzędzia do oceny jakości życia (EQ-5D), podczas gdy istnieje znaczna liczba innych kwestionariuszy, w tym na przykład 36-Item Short Form Survey (SF-36), jej dwunastopunktowy odpowiednik (SF-12) czy Kwestionariusz Oswestry (ODI). Narzędzie EQ-5D zostało wybrane ze względu prostą dla pacjenta formułę, jego powszechny użytek w chirurgii kręgosłupa oraz istniejące tabele użyteczności sprofilowane dla populacji polskiej [44,115,116]. Dodatkowym ograniczeniem tej publikacji była heterogenność badanej grupy pod kątem przyczyny

CCI. Ze względu na rzadkość niestabilności złącza kręgowo-podstawnego, ograniczenie to jest możliwe do zaadresowania jedynie w dużych badaniach wieloośrodkowych.

7. Podsumowanie i wnioski

Dokonana analiza wyników leczenia niestabilności w obrębie złącza kręgowo-podstawnego z wykorzystaniem śrub przeznasadowych w kręgu C2 wskazuje, iż mają one wielowymiarowy charakter. Przeprowadzone i opublikowane badania pozwoliły na wyciągnięcie następujących wniosków:

1. Jako że bezpośrednie, okołooperacyjne wyniki mogą zostać poprawione poprzez brak jatrogennego uszkodzenia tętnicy kręgowej śrubą przeznasadową, kluczowa jest precyzyjna analiza cieśni C2 pod kątem obecności HRVA oraz nasad C2 celem identyfikacji NP. Jak wykazano, te dwa anatomiczne warianty nie są rzadkością zarówno w populacji polskiej, jak i globalnej. Pomiary radiologiczne cieśni i nasad C2 powinny być wykonywane na etapie planowania przedoperacyjnego, gdyż mają wysoką zgodność między różnymi obserwatorami, w obrębie jednego obserwatora w różnych punktach czasowych, a także z wykorzystaniem różnych oprogramowań komputerowych. W przypadku istnienia HRVA i/lub NP, opcją postępowania pozostają śruby translaminarne (przez blaszki łuków), gdyż - jak wykazano - w większości przypadków u tych pacjentów łuki C2 są wystarczającej grubości (Publikacje 1 i 2).
2. Chorzy z reumatoidalnym zapaleniem stawów mają średnio ponad dwukrotnie wyższe ryzyko posiadania HRVA, a co za tym idzie potencjalnie wyższe ryzyko jatrogennego uszkodzenia tętnicy kręgowej i gorszych wyników stabilizacji złącza kręgowo-podstawnego z wykorzystaniem śrub prowadzonych przez nasady C2. Jest to o tyle istotne, iż w tej szczególnej grupie chorych częściej dochodzi do niestabilności w obrębie złącza wymagających stabilizacji (Publikacja 3).
3. W przypadku niestabilności pourazowej najczęściej wykorzystywaną metodą leczenia jest fuzja C1 (masy boczne) – C2 (nasady). Jeśli jednak w tej grupie chorych włączy się potylicę do stabilizacji, a mają oni niestabilność wyłącznie szczytowo-obrotową (C1-C2) bez współistniejącej dyslokacji szczytowo-potylicznej (C0-C1), wówczas wyniki leczenia rozumiane jako stan neurologiczny na wizycie kontrolnej, mogą być gorsze (Publikacja 4).
4. Stabilizacja złącza kręgowo-podstawnego z wykorzystaniem śrub przeznasadowych poprawia jakość życia pacjentów z niestabilnością w obrębie złącza kręgowo-podstawnego, jednak jakość ta nadal jest poniżej dolnego

kwartyla w stosunku do populacji ogólnej dopasowanej do wieku. Predyktorami HRQoL na wizycie kontrolnej po stabilizacji przeznasadowej złącza kręgowo-podstawnego są wiek oraz długość hospitalizacji. Im starszy pacjent oraz im dłużej jest hospitalizowany, tym przewidywalnie będzie miał gorszą jakość życia związaną ze zdrowiem na wizycie kontrolnej. Parametr przedoperacyjnej odległości zęba obrotnika do linii Wackenheima może korelować z HRQoL na wizycie kontrolnej. Dołączenie kości potylicznej do stabilizacji może nie wpływać istotnie na HRQoL (Publikacja 5).

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10. Spis rycin i tabel

Wstęp rozprawy doktorskiej

Publikacja 1

Publikacja 2

Figure 1 Rendition of the sagittal scan through atlantoaxial facetal joint showing measurements of the C2 internal height (*) and C2 isthmus height (**) that are used in the definition of the high-riding vertebral artery. Open access figure from Tomasz Klepinowski et al 2020 [1]. Original Publisher: Springer Nature (Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/).

Figure 2 a Exemplary measurements of C2 pedicle width. Normal width on the right side. Narrow pedicle on the left side. **b** Normal C2 isthmus height (solid line) and C2 internal height (arrow line). c A side with a high-riding vertebral artery. Short C2 isthmus height (solid line). Short C2 internal height (arrow line)

Figure 3 A forest plot of the updated European prevalence of the high-riding vertebral artery. *this study

Table 1 Interobserver, intraobserver, and inter-software agreement coefficients. *reliability categories were defined as follows: < 0.20 poor agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and > 0.80 excellent agreement. HRVA, high-riding vertebral artery. C2P, C2 pedicle

Table 2 Comparison of mean measurements between males and females. C2IsH, C2 isthmus height. C2InH, C2 internal height

Publikacja 3

Figure 1 Sagittal section of atlantoaxial facetal joint. High-riding vertebral artery is defined as isthmus height < 5 mm or/and internal C2 height < 2 mm measured at the level 3 mm lateral to the lateral border of spinal canal. SAF, superior articular facet. IAF, inferior articular facet. VA, vertebral artery. *Internal height. **Isthmus height. Ant., anterior. Post., posterior. Sup., superior. Inf., inferior

Figure 2 A flow diagram depicting the study selection process

Figure 3 A funnel plot illustrating quantitative assessment of the risk of bias

Figure 4 A forest plot of the analyzed studies indicating that rheumatoid arthritis is a risk factor for high-riding vertebral artery

Table 1 Characteristics of the included studies. RA patients with rheumatoid arthritis. HRVA high-riding vertebral artery

Table 2 Tabular display of the Newcastle-Ottawa Scale summarizing qualitative evaluation of the risk of bias. A maximum number of stars that could be awarded was as follows: four for selection, two for comparability, three for outcome

Publikacja 4

Figure 1 A flow diagram depicting the process of including studies into the review and meta-analysis

Figure 2 A graph showing levels of instrumentation that were addressed most frequently. A number of patients with fusion at a given level are shown above the bars

Table 1 PICOS acronym describing characteristics of this review study. AAD, atlantoaxial dislocation; AOD, atlantooccipital dislocation; ASIA, American Spinal Injury Association Impairment Scale; mJOA, modified Japanese Orthopedic Association score; NDI, neck disability index

Table 2 Inclusion and exclusion criteria for the studies screened and checked for eligibility

Table 3 Summarized reviewed studies.

Table 4 Multiple linear regression model to determine factors associated with neurological status at follow-up visits in patients with craniovertebral junction dislocation

Publikacja 5

Figure 1 Distribution of the **(A)** preoperative and **(B)** follow-up domains regarding health-related quality of life in EuroQol-5D questionnaires.

Figure 2 A graph illustrating multiple regression model with two statistically significant predictor variables (age and length of hospital stay). HRQoL – health related quality of life regarded as EuroQol-5 Dimensions-3L summary index.

Table 1 Study group characteristics. CCI – craniocervical instability. HRQoL – health-related quality of life. IQR – interquartile range.

Table 2 EuroQol-5 Dimensions summary indices and Visual Analog Scale in craniocervical instability prior to craniocervical fixation, postoperatively, in comorbidity-matched and age-matched datasets. *Values representing the 25th percentile of the age-matched population. Values are presented as medians unless stated otherwise. Age-matched values are retrieved from the study of Golicki and Niewada.[13] EQ-5D: EuroQol-5 dimensions, CCI: Craniocervical instability, CCJ: Craniocervical junction, VAS: Visual Analog Scale, N/A: Not available

Table 3 Summary of the multiple regression model to predict an outcome variable (health-related quality of life regarded as EQ-5D at follow-up) on the basis of four predictor variables. Statistically significant predictors are bolded.

Table 4 Summary of the pre- and postoperative radiologic evaluation. *Upper number describes rho or P value of the preoperative radiologic parameter, lower number describes rho or P value of the postoperative radiologic parameter. Statistically significant rho/P values are bolded. a: Adults, p: Pediatrics, ADI: Atlantodental interval, rCCI: Revised condyle-C1 interval, BDI: Basion-dens interval, BAI: Basion-axial interval, FM: Foramen magnum, HRQoL: Health-related quality of life.

11. Streszczenie w języku angielskim

Abstract

Introduction: Although craniocervical junction is a durable complex of structures, certain pathological conditions might lead to its dislocation and instability. One of the therapeutic options is to stabilize it by means of screw-rod system utilizing transpedicular C2 screws. Outcomes of this treatment are multimodal and have not been fully studied. In the early perioperative stage, the most important aspect is to maintain vertebral arteries intact. These are at a higher risk of injury in cases of high-riding vertebral arteries (HRVA) and narrow C2 pedicles (NP). Outcome at follow-up, on the other hand, can be appreciated as neurological status and health-related quality of life (HRQoL). Finally, since a post-traumatic subgroup has received little attention in the literature, it is purported that their uniqueness could contribute to a different subset of outcome.

Purpose: (1) To estimate global and regional prevalence of HRVA and NP as they increase a risk of injuring the artery which worsens the immediate outcome. (2) To evaluate whether rheumatoid arthritis increases a risk of HRVA. (3) To find characteristic features of craniovertebral fixation outcomes in a post-traumatic subgroup. (4) To determine clinically relevant data about HRQoL (baseline, at follow-up, correlates, predictors) in subjects fused by means of transpedicular C2 screws.

Methods: Meta-analyses were performed to obtain pooled global, regional, and disease-specific (rheumatoid arthritis) HRVA prevalence. For data on incidence of HRVA and NP in Polish population, a computed tomography-based study was conducted including 383 consecutive cervical spine scans. Kappa statistics for intraobserver, interobserver, and inter-software (Syn.govia versus OsiriX MD) agreement coefficients were calculated. For post-traumatic cohort, a meta-analysis of case reports in literature was conducted encompassing years 2015-2020. EuroQol-5 Dimensions (EQ-5D) questionnaire was used to obtain HRQoL prior to and after CCJ fixation. Spearman's rank correlation rho was sought for classic radiologic measurements and HRQoL at follow-up. In order to determine clinical factors influencing the follow-up HRQoL, multiple linear regression analysis was attempted.

Results: All aims were achieved and published as a series of five full-text articles of a common theme. In publication 1: a meta-analysis of twenty articles including 3126 subjects was performed. The estimated global pooled prevalence of HRVA in subjects

without RA was 20,9% (95% CI 16,5 – 25,8%, I^2 = 87,5%, Cochran's Q = 111,6, p < 0,001). In publication 2: prevalence of HRVA in Polish subjects was 25,3% (95% CI 21,1– 29,8%), whereas at least one NP was seen in 36,8% (95% CI 32,1–41,7%). All coefficients for intraobserver, interobserver, and inter-software agreement were either good or excellent. In publication 3: a meta-analysis of four cohort studies was conducted. A risk ratio of HRVA in patients with RA was estimated at RR = 2,11 (95% CI 1,47 – 3,05, I^2 = 15,19%, Cochran's Q = 3,54, p = 0,32). In publication 4: a meta-analysis of 46 papers involving 141 post-traumatic cases was performed. C1-C2 was fused the most commonly (45,2%), mainly using C2 transpedicular screws. At a mean follow-up of 15,4 months, 27,2% remained neurologically intact. Of those who initially had symptoms, 59% improved, 37% did not change, and 4% worsened. Plating the occiput, especially in those with pure atlanto-axial dislocation, was associated with deterred recovery (β = -0,3; p = 0,023). In publication 5: Median preoperative EQ-5D-3L was 0,186 (IQR = -0,063 to 0,441). At follow-up, on the other hand, it increased to 0,779 (IQR = 0,356 to 0,868). Age and length of hospital stay significantly influenced HRQoL at follow-up (β = -0,004; p = 0,049, and β = -0,134; p = 0,010, respectively). Correlation between preoperative Wackenheim line and post-operative HRQoL was observed (rho = -0,432; p = 0,028).

Conclusions: HRVA is a common variant of VA globally as well as regionally. No significant continental differences were seen for HRVA. Approximately a quarter of Poles have at least one HRVA and more than one-third have one NP. Measurements of HRVA and NP can be consistently reproduced by observers using various software. Thus, craniovertebral fixation ought to be preceded by careful appreciation of HRVA and NP as these abnormalities constitute a risk of injuring the vertebral artery. Rheumatoid arthritis increases the risk of HRVA more than twofold. In post-traumatic subgroup with mere atlanto-axial dislocation, C1-C2 fusion is a treatment of choice, whereas plating the occiput could hinder the rehabilitation deterring the neurological recovery. Baseline HRQoL in subjects with craniovertebral instability is grossly diminished. It can, however, be improved by means of successful fusion. Longer hospital stay and older age at surgery might negatively affect HRQoL at follow-up.

12. Streszczenie w języku polskim

Wstęp: Złącze kręgowo-podstawne jest wytrzymałym kompleksem kostno-więzadłowym, jednak może niekiedy ulec uszkodzeniu i niestabilności. Jedną z opcji terapeutycznych jest stabilizacja z wykorzystaniem śrub przez nasady kręgu C2. Wyniki takiego leczenia mogą być interpretowane wielowymiarowo i jak dotąd nie zostały w pełni zbadane. W okresie okołooperacyjnym najważniejszym aspektem leczenia jest zachowanie tętnic kręgowych w stanie nienaruszonym. Ryzyko ich uszkodzenia jest istotnie zwiększone w przypadku wysoko biegnącej tętnicy kręgowej (HRVA) i wąskich nasad C2 (NP). W dalszej obserwacji wyniki mogą być rozpatrywane jako stan neurologiczny oraz jakość życia związana ze zdrowiem (HRQoL). Unikalną grupą chorych, których wyniki leczenia są słabo poznane, stanowią chorzy z niestabilnością pourazową.

Cel: (1) Oszacować globalną oraz regionalną częstość występowania HRVA oraz NP, jako że zwiększają ryzyko uszkodzenia tętnicy kręgowej, co znacznie pogarsza bezpośrednie wyniki leczenia. (2) Ocenić, czy reumatoidalne zapalenie stawów zwiększa ryzyko HRVA. (3) Wyznaczyć klinicznie istotne dane dotyczące HRQoL (bazowa, w kontroli, korelaty, predyktory) u chorych poddawanych stabilizacji złącza kręgowo-podstawnego. (4) Zidentyfikować charakterystyczne wyniki leczenia w podgrupie pourazowych niestabilności złącza.

Metody: Metaanalizy zostały przeprowadzone celem uzyskania zbiorczej częstości występowania HRVA na poziomie globalnym i regionalnym, a także w przypadku reumatoidalnego zapalenia stawów. Dla określenia częstości HRVA i NP w populacji polskiej, przeprowadzono badanie oparte na ocenie kolejnych 383 badań tomografii komputerowych kręgosłupa szyjnego. Wyznaczono współczynnik kappa Cohena dla oceny zgodności między obserwatorami, wewnątrz obserwatora oraz między oprogramowaniami (Syn.govia versus OsiriX MD). W celu poznania wyników leczenia niestabilności złączka kręgowo-podstawnego w podgrupie pourazowej, przeprowadzono metaanalizę przypadków medycznych opublikowanych w literaturze w latach 2015-2020. HRQoL zostało zmierzone ilościowo stosując kwestionariusz EuroQol-5 Dimensions (EQ-5D). Współczynnik korelacji rang Spearmana został oszacowany w celu identyfikacji korelacji pomiędzy klasycznymi radiologicznymi pomiarami złącza kręgowo-podstawnego a kontrolną HRQoL. Aby określić kliniczne czynniki wpływające

na kontrolną jakość życia związaną ze zdrowiem, przeprowadzono analizę wielorakiej regresji liniowej.

Wyniki: Wszystkie cele zostały osiągnięte i opublikowane jako spójny tematycznie cykl pięciu publikacji. W publikacji 1: wykonano metaanalizę 20 artykułów obejmujących w sumie 3126 uczestników. Oszacowano globalną częstość HRVA u chorych bez reumatoidalnego zapalenia stawów na 20,9% (95% przedział ufności [CI] 16,5 – 25,8%; I2 = 87,5%; Q Cochrana = 111,6; p < 0,001). W publikacji 2: częstość HRVA w populacji polskiej wyniosła 25,3% (95% CI 21,1 – 29,8%), podczas gdy co najmniej jedną NP stwierdzono u 36,8% chorych (95% CI 32,1-41,7%). Wszystkie współczynniki kappa Cohena zgodności dla różnych obserwatorów, wewnątrz jednego obserwatora oraz dla różnych oprogramowań zostały ocenione jako ‘dobre’ lub ‘znakomite’. W publikacji 3: metaanaliza czterech badań kohortowych wykazała, że ryzyko względne wystąpienia HRVA u chorych z reumatoidalnym zapaleniem stawów wynosi 2,11 (95% CI 1,47 – 3,05; I2 = 15,19%, Q Cochrana = 3,54; p = 0,32). W publikacji 4: metaanaliza 46 opublikowanych artykułów zawierających sumarycznie 141 przypadków niestabilności pourazowej w obrębie złącza kręgowo-podstawnego dowiodła, że najczęściej stabilizowanym odcinkiem był C1-C2, głównie przy pomocy śrub prowadzonych przez nasady C2. W okresie obserwacji średnio wynoszącym 15,4 miesiąca, 27,2% chorych pozostało bez deficytów neurologicznych. Z tych, którzy przed operacją miało objawy neurologiczne 59% zaobserwowało poprawę, 37% nie uległo zmianie, zaś u 4% doszło do pogorszenia. Dołączenie potylicy do stabilizacji, zwłaszcza u pacjentów z niestabilnością czysto szczytowo-obrotową, było powiązane z gorszym wynikiem neurologicznych na wizycie kontrolnej (β = -0,3; p = 0,023). W publikacji 5: mediana przedoperacyjnego EQ-5D wyniosła 0,186 (przedział międzykwartylowy [IQR] = -0,063 do 0,441). Z kolei na wizycie kontrolnej wzrosło do 0,779 (IQR = 0,356 do 0,868). Wiek i długość pobytu w szpitalu znacząco wpływały na kontrolne HRQoL (odpowiednio β = -0,004; p = 0,049 oraz β = -0,134; p = 0,010). Zaobserwowano korelację między przedoperacyjnym parametrem Wackenheima a pooperacyjną HRQoL (rho = -0,432; p = 0,028).

Podsumowanie: HRVA jest często występującym wariantem tętnicy kręgowej zarówno globalnie jak i regionalnie (w tym w Polsce). Nie zaobserwowano znaczących różnic międzykontynentalnych. Średnio co czwarty Polak może mieć HRVA i nieco ponad jedna trzecia Polaków może mieć NP. Pomiary HRVA i NP mogą być wiarygodnie powtarzane

przez różnych obserwatorów, przez jednego obserwatora w różnych okresach pomiarów, a także z wykorzystaniem różnych oprogramowań. Dlatego zalecana jest uważna ocena HRVA i NP w procesie planowania przedoperacyjnego celem poprawy wyników leczenia stabilizacją przez nasady C2. Reumatoidalne zapalenie stawów zwiększa ryzyko wystąpienia HRVA ponad dwukrotnie. W podgrupie pourazowej najpowszechniej wykonuje się stabilizację odcinka C1-C2, zaś dołączenie potylicy do stabilizacji w przypadku czystej niestabilności szczytowo-obrotowej może opóźniać lub pogarszać rehabilitację neurologiczną. Bazowe HRQoL u osób z niestabilnością złącza kręgowo-podstawnego jest znacznie obniżone, jednak może być poprawione poprzez zastosowanie stabilizacji przeznasadowej. Podeszły wiek i przedłużona hospitalizacja mogą negatywnie wpływać na HRQoL na wizycie kontrolnej.

13. Załączniki

Załącznik 1 – Przedruk publikacji nr 1

Załącznik 2 – Przedruk publikacji nr 2

Załącznik 3 – Przedruk publikacji nr 3

Załącznik 4 – Przedruk publikacji nr 4

Załącznik 5 – Przedruk publikacji nr 5

Załącznik 6 – Oświadczenia współautorów publikacji

Załącznik 7 – Zaświadczenie Komisji Bioetycznej

13.1 Przedruk publikacji 1

ORIGINAL ARTICLE

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Prevalence of High-Riding Vertebral Artery: A Meta-Analysis of the Anatomical Variant Affecting Choice of Craniocervical Fusion Method and Its Outcome

Tomasz Klepinowski[1], Bartłomiej Pala[1], Jagoda Cembik[2], Leszek Sagan[1]

OBJECTIVE: **A high-riding vertebral artery (HRVA) has been defined as a C2 isthmus height of ≤5 mm and/or internal height of ≤2 mm measured 3 mm lateral to the border of the spinal canal. Its reported prevalence has varied widely. If overlooked during the approach for craniocervical fusion, injury to the vertebral arteries can occur, affecting the outcome. The present meta-analysis aimed to provide the pooled prevalence of HRVAs.**

METHODS: **A comprehensive database search was conducted by 3 of us. Peer-reviewed studies that had followed the strict definition for HRVAs and had reported its prevalence were included. The risk of bias was assessed using the anatomical quality assessment tool. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. The pooled prevalence was calculated using a random effects model.**

RESULTS: **The data from 20 studies with 3126 subjects (7496 sides) were analyzed. The overall pooled prevalence of ≥1 HRVA was 25.3% (95% confidence interval [CI], 19.6%—31.5%). The prevalence in those without the most important confounding factor, rheumatoid arthritis (RA), was 20.9% (95% CI, 16.5%—25.8%). Patients with RA had a prevalence of 42.9% (95% CI, 23.8%—63.1%). The difference between the non-RA and RA groups was statistically significant ($P < 0.001$, test of homogeneity, χ^2). No geographical differences were noted ($P = 0.20$, test of homogeneity, χ^2). Among those with HRVA, unilateral HRVA was present in 70.3% (95% CI, 65.2%—75.2%) and bilateral in 29.7% (95% CI, 24.8%—34.8%). No left or right side predilection was found (left, 50.8%; 95% CI, 33.8%—67.6%; right, 49.2%; 95% CI, 32.4%—66.2%).**

CONCLUSIONS: **Craniocervical fusion should be preceded by examination of the vertebral arteries at the level of C2 because the presence of HRVAs is common and might preclude the safe insertion of transarticular or transpedicular screws.**

INTRODUCTION

The craniocervical junction is a highly specialized unit that enables a great range of motion. Anatomically, it consists of an occipital base, atlas, and axis, with critical neurovascular structures in its immediate proximity. In the case of craniocervical junction dislocation, reduction with fusion might be necessary. During fusion, using either transpedicular or transarticular screws, the vertebral arteries (VAs) can be injured, dramatically affecting the outcome.[1] The estimated risk of this complication is similar for each of these techniques in patients with normal anatomy.[2] Typically, at the level of C2, a VA will enter the transverse foramen and then make a sharp posterolateral turn, exiting the foramen more horizontally than vertically.[3] Therefore, a new phrase for the C2 transverse foramen has been proposed that reflects its 3-dimensional shape—a vertebral artery cave.[4] These curvatures make the VA

Key words
- Atlantoaxial fusion
- C2 isthmus
- Craniocervical fusion
- High-riding vertebral artery
- Transarticular fusion
- Transpedicular fixation
- Vertebral artery anomaly

Abbreviations and Acronyms
CI: Confidence interval
CT: Computed tomography
HRVA: High-riding vertebral artery
RA: Rheumatoid arthritis
VA: Vertebral artery

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prone to an anomalous course, 1 of which is a high-riding vertebral artery (HRVA). The HRVA has been defined as a C2 isthmus height of ≤5 mm and/or an internal height of ≤2 mm measured 3 mm lateral to the border of the spinal canal[2,5] (Figures 1 and 2). The presence of an HRVA, either unilateral or bilateral, will increase the risk of unsuccessful transarticular fixation and, at times, could completely preclude the safe insertion of the screws. If fusion is necessary in a patient with an HRVA, translaminar or spinous process bifid base screws could be applied on that side because they pose a much lower risk of injuring the vessel,[6-8] although they do not have adequate potential for reduction maneuvers. Thus, preoperative awareness and early identification of the HRVA are essential for the choice of the fusion method and the outcome. At present, great discrepancy exists in the reported data regarding the prevalence of this critical variant, from as little as 8.3% to as high as 40.3%.[9,10] The present study aimed to present the evidence-based pooled prevalence of the HRVA.

METHODS

Search Strategy

The following databases were systematically searched independently by 3 of us (T.K., P.B., and J.C.): Web of Science, PubMed MEDLINE, EMBASE, SciELO, and the China National Knowledge Infrastructure. The search terms included "high-riding vertebral artery," "high-riding vertebral groove," high-riding transverse foramen," "C2 isthmus," "high-ride vertebral artery," "HRVA," "axis isthmus," and "axial isthmus." The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses were followed. Titles were imported into Mendeley Desktop, version 1.19.4 (Mendeley, Ltd., London, United Kingdom) and converted into bibliographic data, and the duplicates were removed. Relevant references of the included studies were checked for any studies missed during the primary search.

Eligibility

The inclusion criteria were as follows: 1) data on the prevalence of ≥1 HRVA per person and/or the prevalence of the sides with an HRVA; and 2) the use of the HRVA definition reported by Neo et al.[3] of HRVAs (C2 isthmus height of ≤5 mm and/or an internal height of ≤2 mm measured 3 mm lateral to the border of the spinal canal). Measurements of the isthmus should be taken using the sagittal sections of radiological imaging studies or 3-dimensional reconstructions or the sagittal sections of cadaveric specimens. The exclusion criteria were as follows: 1) studies of cohorts who had undergone solely unilateral C1-C2 transarticular fixation (to avoid a possible bias from a greater risk of a unilateral VA anomaly); 2) studies with overlapping data; 3) case reports; 4) case series with <10 patients; 5), commentaries; 6) conference abstracts; 7) letters to the editor; 8) studies with insufficient data; 9) no definition of HRVA provided; and 10) HRVA definition that was grossly different from that reported by Neo et al.[3] No language restriction was imposed—reports in a language other than English or Polish were translated by fluent speakers of the given language and then evaluated by us. To avoid data overlap, studies by the same investigators were scrutinized more closely to determine whether the period for patient recruitment and/or the inclusion criteria had overlapped.

Data Extraction

We sought to extract the following data: 1) total number of subjects; 2) number of subjects with ≥1 HRVA; 3) number of sides evaluated; 4) number of sides with HRVA; 5) HRVA prevalence stratified by gender; 6) number of patients with rheumatoid arthritis (RA); 7) number of HRVAs in the patients with RA; 8) number of patients without RA in the studies with mixed non-RA and RA populations; 9) number of patients without RA who had had ≥1 HRVA; 10) imaging modality; 11) geographical location; and 12) laterality of the HRVAs. If a report was missing relevant

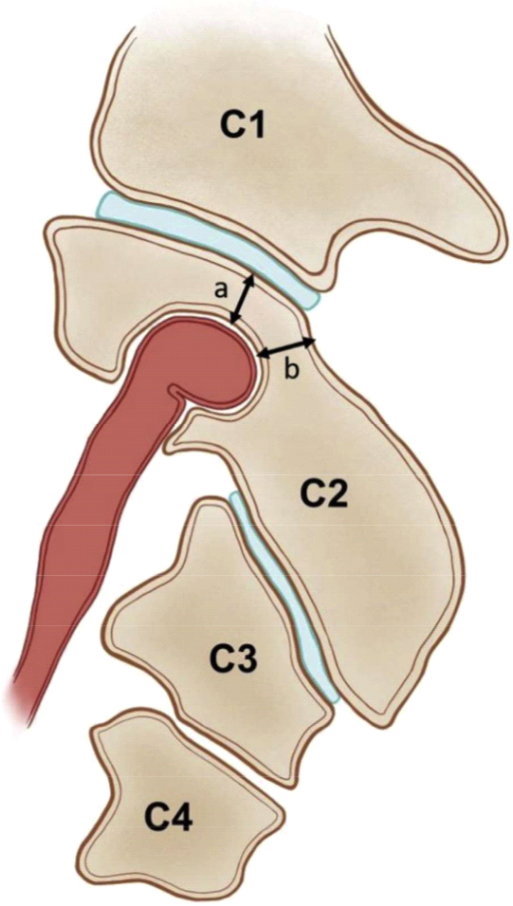

Figure 1. Artist's rendition of the sagittal section through the C2 articular processes: *a*, internal height determined as the shortest distance from the outer margin of the C2 transverse foramen to the surface of the superior articular process; and *b*, isthmus height, defined as the thinnest part of the C2 isthmus.

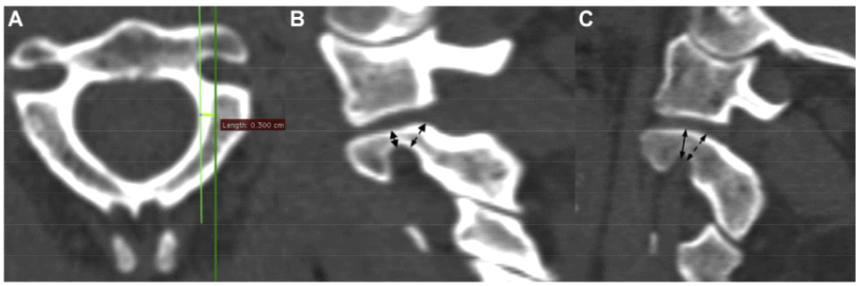

Figure 2. (**A**) Axial computed tomography scan through the C2 transverse processes showing the point 3 mm lateral to the lateral margin of the spinal canal and (**B**) sagittal reconstruction showing the high-riding vertebral artery. *Solid line* indicates the internal height; and *dashed line,* the isthmus height. (**C**) A sagittal slice of the normal transverse foramen without the high-riding vertebral artery.

data (eg, number of affected sides, laterality), the corresponding investigators were queried by e-mail.

Risk of Bias Assessment

A quality check and risk of bias assessment of the anatomical studies included in the present meta-analysis were conducted using the anatomical quality assessment tool.[11] Two of us (T.K., B.P.) used the anatomical quality assessment tool separately for all analyzed studies. If discordance was encountered, a senior coauthor (L.S.) was consulted to reach a consensus. Each study was assessed for 5 domains: 1) objectives and subject characterization; 2) study design; 3) methodology characterization; 4) descriptive anatomy; and 5) reporting of the results. Next, the risk of bias within the domains was recorded as low, high, or unclear. If the answer to a significant question within a domain was "no," consensus was reached regarding whether the entire domain should be considered high risk or low risk. However, if $\geq$2 questions had been answered "no," that domain was instantly recorded as high risk.

Statistical Analysis

Statistical analysis was performed using MetaXL, version 5.3 (EpiGear International Pty., Ltd., Brisbane, Australia) and Statistica, version 13.3.0 (TIBCO Software Inc., Cracow, Poland). For the single-categorical variables, the pooled prevalence was estimated with the corresponding 95% confidence intervals (CIs). Heterogeneity was evaluated using the I^2 and χ^2 values. The I^2 value was interpreted as follows: 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, could represent substantial heterogeneity; and 75% to 100%, considerable heterogeneity present. The level of significance for the Cochrane Q P value was arbitrarily set to <10% ($P < 0.10$). In contrast, the level of significance for the P value of the comparative tests was set to <5% ($P < 0.05$). A random effects model for the meta-analysis of the pooled prevalence was used. The prevalence stratified by geographical regions was compared using a χ^2 test of homogeneity. In addition, differences stratified by gender or the presence of RA were compared using a χ^2 test. Differences in the laterality of HRVA were calculated using the Mann-Whitney U test.

Subgroup Meta-Analysis

In addition to the overall prevalence, we performed subgroup analyses of the presence of HRVA stratified by gender, geographical location, laterality, and the presence of concomitant RA. Because RA has been reported as a possible risk factor for HRVA,[12] it would have been a confounding factor if those patients had been included in the main group without addressing those patients individually. Therefore, the separate analysis for this subgroup had a scientific rationale.

Sensitivity Analysis

The pooled prevalence was estimated with both the RA and the non-RA group included to quantitatively measure the hypothetical influence of RA on the results in the general population.

RESULTS

Inclusion Process and Study Characteristics

The selection process is shown in **Figure 3**. A total of 20 studies had met the eligibility criteria.[2,3,9,10,13-28] The study period for the included studies was from 1997 to 2019. Most of the studies had been performed in Asia (16 of 20; 80%), 2 (10%) had been conducted in North America, and 2 (10%) in Europe (**Table 1**). Of the 20 studies, 14 (70%) had used computed tomography (CT), either classic or with 3-dimensional rendering, 4 had used angiographic CT (20%), and 2 studies were cadaveric (10%). The 20 studies included 3126 patients and 7496 sides with a known status of the C2 transverse foramen (HRVA vs. non-HRVA).

Quality and Risk of Bias

The greatest risk of bias for the included studies regarded the method used, with 12 of the 20 having a high risk of bias. The high risk had mainly resulted from the lack of appropriate measures taken to reduce inter- and intraobserver variability, no report of the specialty and/or experience of those assessing the imaging

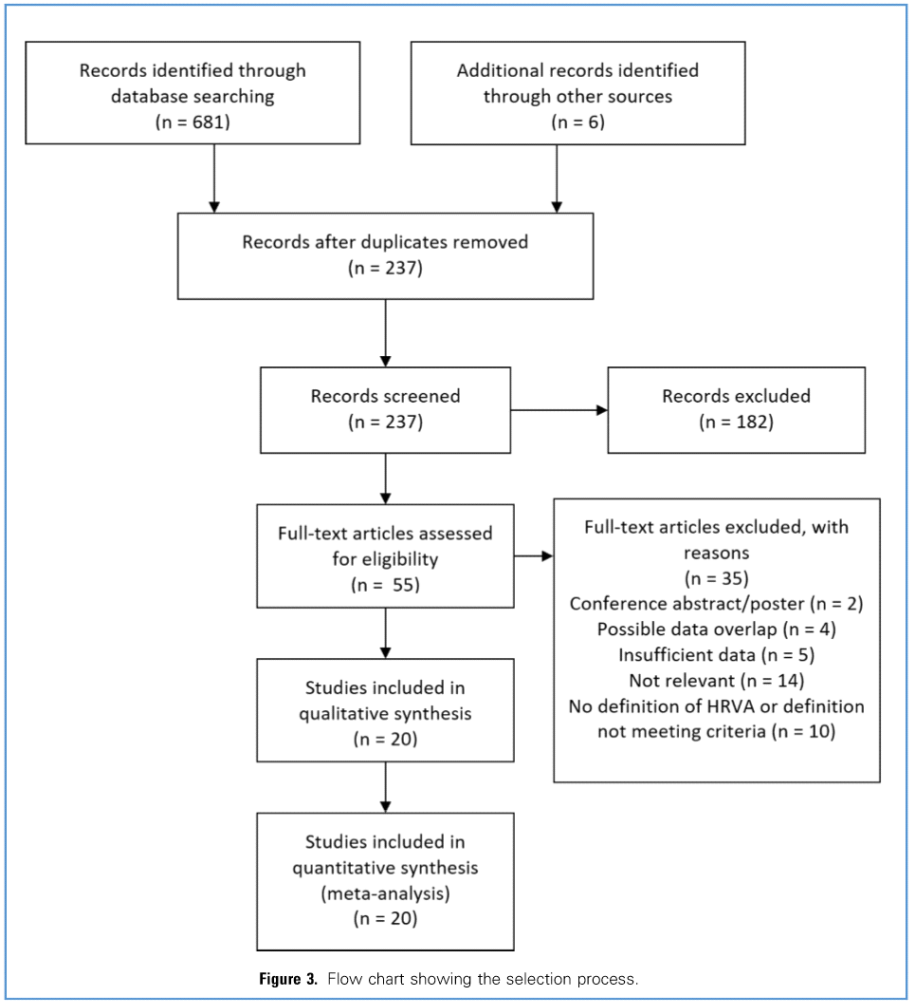

Figure 3. Flow chart showing the selection process.

studies, and no details provided of the manufacturers of the equipment used. In the other domains, the risk of bias was mostly low owing to the strict criteria we had used for eligibility. Of the 20 studies, 16 had had a low risk in terms of the objectives and study characteristics, 19 had had a low risk in the study design and descriptive anatomy, and 14 had had a low risk of bias in the reporting of their results (Table 2).

HRVA Prevalence

The random effects model yielded a pooled prevalence of 20.9% (95% CI, 16.5%–25.8%; $I^2 = 87.5\%$; Cochran Q = 111.6; $P < 0.001$) for those without RA (Figure 4). The overall prevalence with both non-RA and RA groups included was 25.3% (95% CI, 19.6%–31.5%; $I^2 = 92.3\%$; $P < 0.001$). Of the 20 studies, 19 ($n = 5636$ sides) had provided complete data on the side prevalence, which was estimated at 18.5% (95% CI, 15.1%–22.0%; $I^2 = 90.5\%$; $P < 0.001$). The 14 studies that had analyzed 3990 sides without RA had reported a prevalence of 16.7% (95% CI, 12.7%–21.0%; $I^2 = 91.2\%$; $P < 0.001$).

Subgroup and Sensitivity Analysis

Regarding the geographical location, the prevalence of HRVAs in non-RA subjects was the greatest among Europeans (23.93%; 95% CI, 20.49%–27.55%), followed by Asians (21.48%; 95% CI, 15.96%–27.56%) and North Americans (19.17%; 95% CI, 2.76%–43.20%). The difference, however, did not reach statistical significance ($P = 0.20$, χ- test of homogeneity) possibly because of the low number of studies from outside of Asia (Table 3). Among the patients with RA, an HRVA was present in 42.91% (95% CI, 23.79%–63.11%; $I^2 = 64.68\%$; Cochran's Q = 8.49). The difference between the RA and non-RA groups was statistically significant ($P < 0.001$, χ^2 test). Overall, women were more likely

Table 1. Summary of Included Studies

Study	Geographical Location	Imaging Modality	Subjects; Sides (*n*)	HRVA Prevalence Overall (%)	Prevalence of Sides with HRVA (%)
Abou Madawi et al.,[13] 1997	Europe	Cadaveric	50; 100	22	14
Ankith et al.,[14] 2019	Asia	CT	930; 1860	11.6	8.1
Chung et al.,[9] 2005	Asia	CT	67; 134	40.3	26.5
Elgafy et al.,[15] 2014	North America	CT	100; 200	32	21
Higashino et al.,[16] 2009	Asia	CT	129; 258	26.4	26
Kim et al.,[17] 2008	Asia	CT	166; 332	22.3	14.5
Kothari et al.,[18] 2019	Asia	CT	210; 420	20.0	14.0
Lee et al.,[19] 2017	Asia	CT	180; 360	40.0	27.2
Lee et al.,[20] 2007	Asia	CT	12; 24	25.0	16.7
Li et al.,[10] 2017	Asia	CT	72; 144	8.3	4.2
Li et al.,[21] 2019	Asia	Angiographic CT	120; 240	NR	31.25
Maki et al.,[22] 2016	Asia	Angiographic CT	100; 200	28.0	17.0
Mandel et al.,[23] 2000	North America	Cadaveric	205; 410	11.7	6.6
Moon et al.,[24] 2018	Asia	Angiographic CT	100; 200	31.0	23.0
Neo et al.,[3] 2005	Asia	CT	43; 86	23.3	14.0
Park et al.,[28] 2019	Asia	CT	251; 502	35.9	24.5
Pruthi et al.,[25] 2018	Asia	CT	33; 66	NR	37.9
Vaněk et al.,[26] 2017	Europe	Angiographic CT	511; 1022	24.1	15.0
Wajanavisit et al.,[27] 2016	Asia	CT	200; 400	NR	16.5
Yeom et al.,[2] 2013	Asia	CT	269; 538	NR	14.5

HRVA, high-riding vertebral artery; CT, computed tomography; NR, not reported.

to have ≥1 HRVA (26.82%; 95% CI, 19.58%–34.73%) than were men (15.20%; 95% CI, 8.16%–23.84%; P = 0.0016, χ^2 test). However, with removal of the most confounding factor, the presence of RA, the gender difference was not statistically significant (P = 0.45). In terms of laterality, the left side was affected at a similar rate as the right side (left side, 50.8%; 95% CI, 33.8%–67.6%; right side, 49.2%; 95% CI, 32.4%–66.2%; P = 1.0, Mann-Whitney U test). Twelve studies (n = 584) had assessed the laterality of HRVA dichotomously (unilateral vs. bilateral) and reported that in the case of HRVAs, a unilateral HRVA was present in 69.0% (95% CI, 64.0%–73.9%) and bilateral in 31.0% (95% CI, 26.1%–36.0%; I^2 = 32.60; P = 0.129).

DISCUSSION

The reported data have provided a wide range of prevalence of HRVAs, with a range from 8.3% to ≤40%. However, the results from the present meta-analysis have demonstrated that the 95% CI of the prevalence in the general population without RA ranges from 16.5% to 25.8%. This prevalence should be considered when treating patients who require craniocervical fusion, using either transpedicular or transarticular screws, because it has been proved that the presence of an HRVA increases the risk of injury with both techniques and to a greater extent for the latter. The reason a narrow C2 isthmus, a fundamental principle of the HRVA definition, also affects transpedicular fixation was clarified by Naderi et al.[29] in 2004. They reported evidence of intimate relationships between the isthmus and pedicle and suggested a common name—the pediculoisthmic component.[29]

RA and HRVA

The results from the present meta-analysis have confirmed the findings from previous reports that the presence of RA is a risk factor for HRVA.[12] The proposed pathophysiology for this association is the constant throbbing force against the osteoporotic and chronically inflamed bone, leading to thinning of the isthmus and shortening of the internal height.[26] In the present study, the estimated prevalence of an HRVA in patients with RA was 42.9% (95% CI, 23.8%–63.1%) and was significantly greater compared with that in the patients without RA (20.9%; 95% CI, 16.5%–25.8%). It remains unknown whether the disease duration or the use of concomitant steroid therapy has an effect on the development of HRVAs. Furthermore, the HRVA prevalence might vary depending on the RA stage. These, possibly confounding, factors could be

Table 2. Summary of Risk of Bias Assessment Using an Anatomical Quality Assessment Tool

Investigator	Risk of Bias				
	Objectives and Study Characteristics	Study Design	Methodology	Descriptive Anatomy	Reporting of Results
Abou Madawi et al.,[13] 1997	High	Low	High	Low	Low
Ankith et al.,[14] 2019	Low	Low	High	Low	High
Chung et al.,[9] 2005	Low	Low	High	Low	Low
Elgafy et al.,[15] 2014	Low	Low	Low	Low	Low
Higashino et al.,[16] 2009	Low	Low	Low	Low	Low
Kim et al.,[17] 2008	Low	Low	High	Low	Low
Kothari et al.,[18] 2019	Low	Low	Low	Low	Low
Lee et al.,[19] 2017	Low	Low	High	High	Low
Lee et al.,[20] 2007	High	Low	High	Low	High
Li et al.,[10] 2017	Low	Low	Low	Low	Low
Li et al.,[21] 2019	Low	Low	Low	Low	High
Maki et al.,[22] 2016	Low	Low	Low	Low	Low
Mandel et al.,[23] 2000	Low	Low	High	Low	Low
Moon et al.,[24] 2018	Low	High	High	Low	Low
Neo et al.,[3] 2005	High	Low	High	Low	High
Park et al.,[28] 2019	Low	Low	High	Low	High
Pruthi et al.,[25] 2018	High	Low	High	Low	High
Vaněk et al.,[26] 2017	Low	Low	Low	Low	Low
Wajanavisit et al.,[27] 2016	Low	Low	Low	Low	Low
Yeom et al.,[2] 2013	Low	Low	High	Low	Low

addressed in future research. In addition, the presence of RA significantly affected the prevalence of HRVAs in women because they develop RA much more frequently than do men. With removal of RA from the gender subgroup analysis, the relevant difference diminished to a nonsignificant level (P value increased from 0.0016 to $\leq$ 0.45).

Laterality

Although the study by Vaněk et al.[26] had reported a significant dominance of the left side in HRVA prevalence, the results from the present meta-analysis found no such difference (left, 50.8%; 95% CI, 33.8%–67.6%; right, 49.2%; 95% CI, 32.4%–66.2%; P = 1.0, Mann-Whitney U test). However, we have also confirmed the findings from previous reports that unilateral HRVA is >2 times more common than the bilateral variant (69.0% vs. 31.0%).

Guide for Clinical Decision-Making

Once a patient has been scheduled for craniocervical fusion, a cervical spine CT scan and CT angiogram should be obtained. Both the C2 isthmi and pedicles should be appreciated and measured. Next, the side dominance of the VA should be determined. The following scenarios can be encountered and could affect the choice of the craniocervical fusion method:

1. Unilateral HRVA with an ipsilateral dominant VA: on the HRVA side, a transarticular screw will be precluded. The use of a

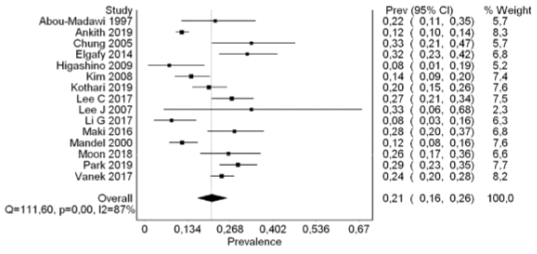

Figure 4. Forest plot of random effects model demonstrating pooled prevalence (Prev) of the high-riding vertebral artery in subjects without rheumatoid arthritis (20.9%; 95% confidence interval [CI], 16.5%–25.8%; I^2 = 87.5%; Cochran Q = 111.6; $P < 0.001$).

Table 3. Juxtaposition of Overall Prevalence, Sensitivity, and Subgroup Analysis

Subgroup	No. of Studies (No. of Subjects)	Pooled Prevalence of HRVA (%; 95% CI)	I^2 Heterogeneity (%)	*P* Value of Cochran Q
Overall, including RA patients	16 (3126)	25.3 (19.6–31.5)	92.3	<0.001
Overall sides, including RA	20 (7496*)	17.8 (14.3–21.7)	93.8	<0.001
Only RA patients	4 (125)	42.9 (23.8–63.1)	64.7	0.037
Laterality	9 (385)		82.8	<0.001
Left		36.4 (23.3–48.9)		
Right		36.3 (23.2–48.8)		
Bilateral		27.3 (15.7–39.4)		
Gender				
Female	6 (390)	26.8 (19.6–34.7)	60.2	0.028
Male	5 (432)	15.2 (8.2–23.8)	76.4	0.002
Geographical region				
Asia	12 (2168)	21.5 (16.0–27.6)	88.3	<0.001
North America	2 (305)	19.2 (2.8–43.2)	94.1	<0.001
Europe	2 (561)	23.9 (20.5–27.6)	0.0	0.80
Overall without RA	15 (2934)	20.9 (16.5–25.8)	87.5	<0.001
Overall sides without RA	15 (5850*)	15.9 (12.0–20.3)	93.8	<0.001

HRVA, high-riding vertebral artery; CI, confidence interval; RA, rheumatoid arthritis.
*Number of sides.

transpedicular screw will also result in an increased risk of dominant VA injury. However, it can be placed with extreme caution and using intraoperative navigation. The use of an ipsilateral translaminar screw is an acceptable safe option.

2. Unilateral HRVA with a contralateral dominant VA: on the HRVA side, a transarticular screw will be precluded. The use of bilateral transpedicular screws is possible and has often been used as long as the pedicles are not narrow. However, the use of an ipsilateral translaminar screw might be the safer option.
3. Bilateral HRVA: for bilateral HRVAs, the use of transarticular screws is precluded. The use of transpedicular screws will also be risky, especially on the side of the dominant VA. However, with the aid of intraoperative navigation, screw placement will usually be possible. The use of bilateral translaminar screws will be the safest rescue option for bilateral HRVAs.
4. Bilateral non-HRVA: the use of transarticular or transpedicular screws is acceptable and will provide the best fixation.

Study Limitations

Although comprehensive, the present study was not free of limitations. Most of the included studies had a high risk of methodological bias because little information was available regarding the software, manufacturers of the equipment used, or investigators' specialties, In addition, because most of the data was from Asia, the global prevalence of HRVAs might differ slightly according to geographical location. We found that the studies from Australia, Africa, and South America had not reported any measurements. Moreover, the present meta-analysis found only 2 studies from Europe and 2 studies from North America that had met our inclusion criteria. Several potentially contributory reports had had to be eliminated because they had used grossly different or ambiguous definitions of HRVAs or no definition at all. Examples of these definitions included "maximal screw diameter $\leq$4 mm" and "transverse foramen on the path of the ideal screw trajectory," which were deemed too risky of bias. Hence, we would recommend that more well-designed studies using a unanimous definition of HRVAs be conducted in these regions.

CONCLUSIONS

Determining the best approach for craniocervical fusion should be preceded by examination of the patient's VA course, especially at the C2 level, because the HRVA has been shown to be common and its presence might preclude safe insertion of transarticular or transpedicular screws. Patients with RA had a greater prevalence of HRVAs. Further research, minimizing methodological bias, could provide more evidence and a greater understanding of this critical anatomical variant that can affect the outcomes of the craniocervical fusion.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Tomasz Klepinowski: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing - original draft, Writing - review & editing.

Bartłomiej Pala: Data curation, Investigation, Writing - original draft. **Jagoda Cembik:** Data curation, Investigation, Visualization, Software. **Leszek Sagan:** Formal analysis, Supervision, Validation, Writing - review & editing.

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ORIGINAL ARTICLE

Prevalence of high-riding vertebral arteries and narrow C2 pedicles among Central-European population: a computed tomography-based study

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Abstract
High-riding vertebral artery (HRVA) and narrow C2 pedicles (C2P) pose a great risk of injuring the vessel during C2 pedicle or transarticular screw placement. Recent meta-analysis revealed a paucity of European studies regarding measurements and prevalence of these anatomical variants. Three hundred eighty-three consecutive cervical spine CT scans with 766 potential screw insertion sites were analyzed independently by two trained observers. C2 internal height (C2InH), C2 isthmus height (C2IsH), and C2P width were measured. Kappa statistics for inter- and intraobserver reliability as well as for inter-software agreement were calculated. HRVA was defined as C2IsH of ≤ 5 mm and/or C2InH of ≤ 2 mm. Narrow C2P was defined as C2P width ≤ 4 mm. STROBE checklist was followed. At least 1 HRVA was found in 25,3% (95% CI 21,1–29,8) of patients (16,7% of potential sites). At least 1 narrow C2P was seen in 36,8% (95% CI 32,1–41,7) of patients (23,8% of potential sites). Among those with HRVA, unilateral HRVA was present in 68,0% (95% CI 58,4–77,0), whereas bilateral HRVA in 32,0% (95% CI 23,0–41,6). No difference in terms of laterality (right or left) was seen neither for HRVA nor narrow C2P. Significant differences were found between females and males for all measurements. Each parameter showed either good or excellent inter- or intraobserver, and inter-software agreement coefficients. HRVA and narrow C2P are common findings in Central-European population and should be appreciated at the planning stage before craniocervical instrumentation. Measurements can be consistently reproduced by various observers at varying intervals using different software.

Keywords High-riding vertebral artery · Narrow pedicles · C2 isthmus · Craniocervical fusion · Prevalence

Introduction

Craniocervical junction (CCJ) is considered a tiger land in neurosurgery. Proximity of vitally important structures makes it difficult to approach. If instrumentation is planned, meticulous attention is paid to the course of vertebral arteries (VAs) and to the width of C2 pedicles. VA course presents many anatomical variations, some of them particularly affecting choice and outcome of craniocervical fusion [8]. A high-riding vertebral artery (HRVA) has been defined as a C2 isthmus height (C2IsH) of ≤ 5 mm and/or C2 internal height (C2InH) of ≤ 2 mm at the level 3 mm lateral to the border of the spinal canal [10, 11]. The presence of this anomaly increases the risk of vascular injury during CCJ instrumentation, far lateral, or extreme lateral approaches to the CCJ [2, 3]. Recent meta-analysis of global HRVA prevalence highlighted gaps in the literature as 16 of 20 analyzed studies came from Asia and only two were of European origin [8]. Given the fact that body height and genetics differ significantly between Asian and European subjects, it is rationalized to hypothesize that craniocervical and cervical measurements might be distinct in these populations [4, 13]. Prevalence of ossification of posterior longitudinal ligament is a good example of such discrepancy in cervical spine between the aforementioned regions [5]. Hence, HRVA and narrow C2 pedicle incidence should be specified in various human races. Therefore, this study aims to provide a response to that relevant remark, aiding the body of neurosurgical literature.

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Methodology

Study design

A retrospective observational study of 383 consecutive anonymized computed tomography (CT) scans meeting inclusion criteria was analyzed by two independent observers. All the scans were made due to medical indications, none solely for the sake of this research. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was followed to ensure the correct structure. Each item of the STROBE was addressed.

Sample size estimation

Assuming probability of type I error at 5% ($\alpha = 0{,}05$) and the desired type II error at 20% ($\beta = 0{,}2$) with statistical power of the study being arbitrarily set at 80%, the minimum sample size has been estimated at 383 subjects (766 potential screw insertion sites) in order to be representative of the general thirty-eight million people Polish population in the region of Central Europe.

Patient selection

Inclusion criteria were as follows: (1) adults, (2) CT scan of the cervical spine with adequate visualization of the atlas and axis, and (3) correct reformatting of the scans into the sagittal section. On the other hand, patients were excluded from the study in case of (1) instrumentation of the upper cervical spine, (2) any fracture of the C2 vertebra, (3) age less than 18 years, (4) inadequate quality of the study due to excessive motion or other technical issues, and (5) rheumatoid arthritis.

Software and measurements

All CT scans were obtained using Somatom Sensation 64 (Siemens Healthineers, Erlangen, Germany). Syn.govia (Siemens Healthineers, Erlangen, Germany) was employed for the primary measurements. Sagittal imaging was utilized for HRVA identification, whereas axial scans were used for pedicle appreciation. HRVA is declared present if C2IsH was ≤ 5 mm and/or C2InH was ≤ 2 mm measured 3 mm lateral to the border of the spinal canal (Fig. 1 and Fig. 2). Pedicles are deemed narrow if their width was ≤ 4 mm (Fig. 2). OsiriX MD 11.0 (Pixmeo SARL, Bernex, Switzerland) was used for secondary measurements in order to establish inter-software agreement. In order to determine whether rescue laminar screws are an option for subjects with bilateral HRVA or/and bilateral NP, laminar thickness was measured only in those individuals. Thin C2 lamina was defined as laminar thickness < 4 mm measured on axial CT scans.

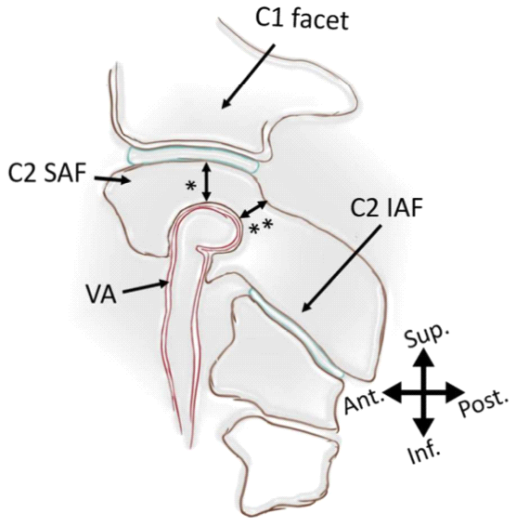

Fig. 1 Rendition of the sagittal scan through atlantoaxial facetal joint showing measurements of the C2 internal height (*) and C2 isthmus height (**) that are used in the definition of the high-riding vertebral artery. Open access figure from Tomasz Klepinowski et al 2020 [1]. Original Publisher: Springer Nature (Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/)

Interobserver, intraobserver, and inter-software variabilities

In order to determine interobserver variability, investigator triangulation was employed: two trained observers (neurosurgical resident TK and radiologic resident NŻ) were presented with a uniform PowerPoint slideshow (Microsoft, Redmond, USA) illustrating measurement methodology as well as caveats of possibly difficult cases to ensure harmonious technique. The slideshow was ended with a preliminary test of ten exemplary cases, followed by debriefing and a question-and-answer session afterward. For quantitative assessment of interobserver reproducibility, kappa statistic (κ_1) evaluating agreement between TK and NŻ was calculated. On the other hand, intraobserver variability was established by re-measuring cases after a period of two to three months. For this, another kappa statistic (κ_2) was calculated. For estimation of inter-software agreement coefficient, the same cases were re-measured using another software—OsiriX MD 11.0 (Pixmeo SARL, Bernex, Switzerland).

Statistical analysis

Statistical analysis was performed by means of Statistica 13.3.0, TIBCO Software Inc. (Palo Alto, California, USA)

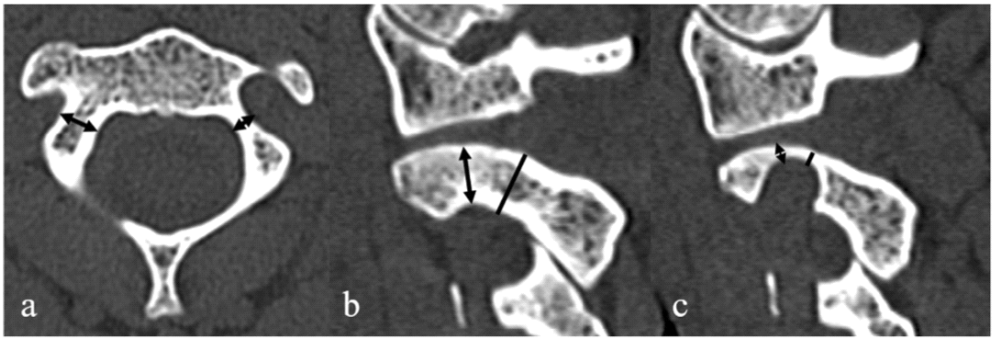

Fig. 2 **a** Exemplary measurements of C2 pedicle width. Normal width on the right side. Narrow pedicle on the left side. **b** Normal C2 isthmus height (solid line) and C2 internal height (arrow line). **c** A side with a high-riding vertebral artery. Short C2 isthmus height (solid line). Short C2 internal height (arrow line)

and MetaXL 5.3 (EpiGear International Pty., Ltd., Brisbane, Australia). The level of significance for the *P* value of the comparative tests was arbitrarily set to < 5% ($P < 0.05$). To check for normality, a Shapiro-Wilk test was used. Welch's *t* test was employed to determine variances. Pearson's chi-square test was applied for categorical variables, whereas for continuous variables Student *t* for independent samples (in normal distribution) and Wilcoxon-Mann-Whitney (in non-normal distributions) tests were used. Possible values for kappa are within a range from – 1 to 1, with 0 tantamount to randomness, and 1 suggesting perfect reproducibility. As generally accepted, interpretation of the kappa values was as follows: < 0.20 poor agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and > 0.80 excellent agreement.

Results

Subject characteristics

A total of 383 cervical spine CT scans were analyzed comprising 766 potential screw insertion sites. There were 237 females (61,9%) and 146 males (38,1%). Mean age of the cohort was 43,2 years (range 22–86 years). As determined by eligibility criteria, none of the subjects had neither fractures within craniocervical junction, past procedure with cervical instrumentation, nor rheumatoid arthritis.

Interobserver, intraobserver, and inter-software reliability coefficients

Assessment revealed that interobserver reliability of the left HRVA, right HRVA, left pedicle width, and right pedicle width was excellent (κ = 0,848), excellent (κ = 0,873), good (κ = 0,784), and good (κ = 0,784), respectively. Intraobserver reliability was found excellent for all four measurements with the following kappa statistics: κ = 0,852, κ = 0,834, κ = 0,864, and κ = 0,912 for the left HRVA, right HRVA, left pedicle width, and right pedicle width, respectively. Inter-software agreement between Syn.govia and OsiriX was excellent for the left HRVA (κ = 0,940), good for the right HRVA (κ = 0,703), excellent for the left pedicle width (κ = 0,896), and good for the right pedicle width (κ = 0,774). Summary of the agreement evaluation is presented in Table 1.

Measurements and prevalence of high-riding vertebral arteries and narrow pedicles

Mean left C2IsH was 7,4 mm (SD ± 2,4 mm). Mean right C2IsH was 7,9 mm (SD ± 2,5 mm). Mean left C2InH was 6,7 mm (SD ± 2,6 mm). Mean right C2InH was 7,4 mm (SD ±

Table 1 Interobserver, intraobserver, and inter-software agreement coefficients

Measurement	Cohen's kappa statistic (κ)	Reliability category*
Interobserver		
Left HRVA	0.848	Excellent
Right HRVA	0.873	Excellent
Left narrow C2P	0.784	Good
Right narrow C2P	0.795	Good
Intraobserver		
Left HRVA	0.852	Excellent
Right HRVA	0.834	Excellent
Left narrow C2P	0.864	Excellent
Right narrow C2P	0.912	Excellent
Inter-software		
Left HRVA	0.940	Excellent
Right HRVA	0.703	Good
Left narrow C2P	0.896	Excellent
Right narrow C2P	0.774	Good

*reliability categories were defined as follows: < 0.20 poor agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and > 0.80 excellent agreement. *HRVA*, high-riding vertebral artery. *C2P*, C2 pedicle

2,7). Mean left C2P width was 5 mm (SD ± 1,5 mm). Mean right C2P width was 5,4 mm (SD ± 1,6 mm). Prevalence of at least one HRVA was calculated to be 25,3% (95% CI 21,1–29,8) of subjects and 16,7% (95% CI 14,2–19,4) of potential screw insertion sites. Among individuals with HRVA, unilateral HRVA was present in 68,0% (95% CI 58,4–77,0), whereas bilateral HRVA was seen in 32,0% (95% CI 23,0–41,6). There was no statistically significant difference in terms of laterality: the left side showed prevalence of 56,6% (95% CI 47,9–65,1), and the right was found in 43,4% (95% CI 34,9–52,1). In male, at least 1 HRVA was seen in 16,4% (95% CI 10,8–22,9), whereas in female in 30,8% (95% CI 25,1–36,8). Prevalence of at least one C2 narrow pedicle was 36,8% (95% CI 32,1–41,7) of patients and 23,8% (95% CI 20,8–26,8) of potential screw insertion sites. Unilateral NP was present in 70,9% (95% CI 63,1–78,2), whereas bilateral NP was found in 29,1% (95% CI 21,8–36,9). Among those with NP, there was no significant side predilection: left 55,4% (95% CI 48,2–62,6) vs right 44,6% (37,4–51,8). As for gender predisposition, 30,8% (95% CI 23,6–38,6) of men and 40,5% (95% CI 34,3–46,8) presented NP. Relevant mean values of measurements in men and women differ significantly (Table 2).

Laminar thickness measurements for rescue screws

Among the subjects with bilateral HRVA, mean thickness of the left lamina was 5,48 mm (SD ± 1,21) on the left and 5,33 mm (SD ± 0,97) on the right with only four (13,3%) and three (10%) being thin (< 4 mm), respectively. In subjects with bilateral NP, mean left C2 laminar thickness was 5,49 mm (SD ± 1,06), whereas for the right, it was 5,45 mm (SD ± 0,83) with only 3 (7,3%) and 1 (2,4%) being thin, respectively.

Discussion

The results of this CT-based study confirm that high-riding vertebral arteries and narrow C2 pedicles are relatively common. As global prevalence of HRVA has been estimated at 20,9% (95% CI 16,5–25,8%), the findings of this paper fit into the given confidence interval. Global prevalence of narrow C2P has not been studied, yet. However, its prevalence that was delineated here appears to be higher than showed by Asian researchers (Yeom et al in 2013) among Korean population (23,8% vs 9,5% of potential screw insertion sites). Possible explanation might be regional ethnical differences in the anatomy of high cervical spine [4].

Table 2 Comparison of mean measurements between males and females

Measurement	Male [mm]	Female [mm]	*P*
Left C2IsH	8,3	6,2	< 0,001
Left C2InH	7,5	6,9	< 0,001
Right C2IsH	8,8	7,4	0,02
Right C2InH	8,2	6,9	< 0,001
Left C2 pedicle width	5,4	4,8	< 0,001
Right C2 pedicle width	5,7	5,2	< 0,001

C2IsH C2 isthmus height. *C2InH* C2 internal height

Updated European prevalence of HRVA

Klepinowski et al. in 2020 conducted a comprehensive meta-analysis which presented global prevalence of HRVA. However, the regional prevalence analysis was of a limited value because of the small number of European studies. In fact, only two European papers were found eligible at that time, with one greatly outweighing the other. Therefore, the authors decided to aid the body of neurosurgical literature and proceed with the high-quality study. Including the present paper (Klepinowski 2021*), the updated European prevalence of at least one HRVA among a total of 944 subjects [1, 12] is now estimated at 24,52% (95% CI 21,83–27,32, I^2 = 0,0 [0–32,7], Cochran Q = 0,31; random-effects model) (see Fig. 3). Comparing to the previously estimated prevalence, the updated one has narrower confidence interval, and the weight is more evenly distributed across the studies.

Clinical implications

As it was recently noted, the most commonly employed method of managing both post-traumatic and rheumatic craniovertebral dislocation is Goel-Harms C1 lateral mass-C2 pedicle screw placement [6, 7]. This procedure has become a gold standard thanks to polyaxial screws that provide a solid bicortical purchase. Yet it is imperative to pay close attention preoperatively to two critical aspects: course of vertebral arteries and width of C2 pedicles. Practical guidelines for choice of craniocervical fusion method in case of HRVA have been published by the authors elsewhere [8]. The same pertains to the presence of C2 narrow pedicles, which may preclude safe screw placement. In those instances, rescue translaminar screws, laminar hooks, or spinal navigation might come in handy. As shown, most of the subjects even with bilateral HRVA or NP have normal C2 laminar thickness (≥ 4 mm), indicating that there usually exists a viable rescue option. Moreover, if HRVA or NP is identified early on the preoperative planning stage, additional steps might be taken to reduce a risk of injuring the VA. For instance, one may utilize intraoperative Doppler ultrasound as was elegantly demonstrated by Lofrese et al [9]. This can smoothly guide a spine surgeon through the procedure by delineating safe and danger zones where the VA could be inadvertently damaged. Therefore, combining the new information from the present

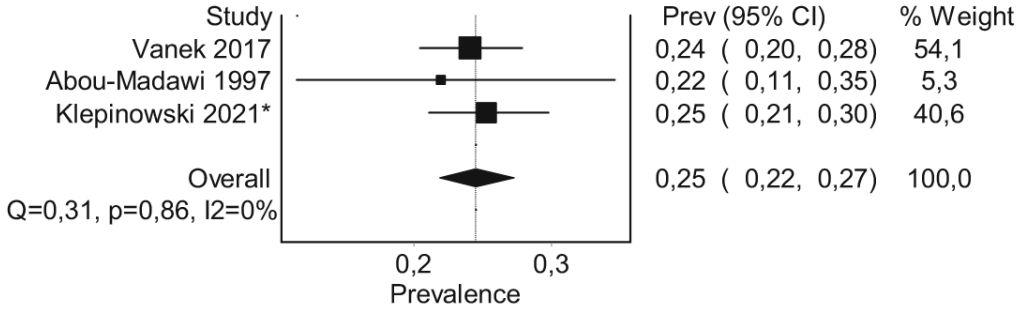

Fig. 3 A forest plot of the updated European prevalence of the high-riding vertebral artery. *this study

study with already existing literature may further increase safety of the C1-C2 fusion and improve the overall outcome.

Limitations

Although executed with attention to details and focused on quality, this study is not free from limitations. In spite of the intraobserver reliability being excellent across all the measurements, the interobserver and inter-software agreement coefficients were only good for both pedicle sides (interobserver) and for the right HRVA along with the right pedicle width (inter-software). This means the overall prevalence might slightly differ between clinicians planning the craniocervical instrumentation. This might also partially account for differences between researchers across the continents, yet ethnic background and genetics constitute a more probable cause.

Conclusions

A quarter of Central-European population have at least one HRVA, and about one-third of Central-Europeans have at least one narrow C2 pedicles (a quarter of potential screw insertion sites). There is no side predilection. In general, men appear to have larger C2 isthmi and C2 pedicles than women. Measurements can be consistently reproduced by various observers at varying intervals using different software. Thus, both HRVA and narrow C2 pedicles should be looked for at the planning stage prior to craniocervical instrumentation in order to choose the safest treatment option.

Authors' contribution **TK**–conceptualization; methodology; validation; formal analysis; resources; data curation; writing; original draft; writing, review and editing; project administration. **NŻ**–methodology, investigation. **BP**–investigation, writing, original draft. **WP**–supervision, validation. **LS**–supervision, validation

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Availability of data and material (data transparency) The data that support the findings of this study are available from the corresponding author, TK, upon reasonable request.

Code availability (software application or custom code) Not applicable

Declarations

Ethics approval For this kind of retrospective study no ethics approval was required

Consent for publication (include appropriate statements) Authors of this study grant the Publisher the sole and exclusive license of the full copyright.

Consent to participate As this was a retrospective analysis of the studies that had been published in the past, no consent to participate was necessary.

Conflict of interest The authors declare that they have no conflict of interest.

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REVIEW

Risk of the high-riding variant of vertebral arteries at C2 is increased over twofold in rheumatoid arthritis: a meta-analysis

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Abstract
Rheumatoid arthritis (RA) might lead to atlantoaxial instability requiring transpedicular or transarticular fusion. High-riding vertebral artery (HRVA) puts patients at risk of injuring the vessel. RA is hypothesized to increase a risk of HRVA. However, to date, no relative risk (RR) has been calculated in order to quantitatively determine a true impact of RA as its risk factor. To the best of our knowledge, this is the first attempt to do so. All major databases were scanned for cohort studies combining words "rheumatoid arthritis" and "high-riding vertebral artery" or synonyms. RA patients were qualified into the exposed group (group A), whereas non-RA subjects into the unexposed group (group B). Risk of bias was explored by means of Newcastle-Ottawa Scale. MOOSE checklist was followed to ensure correct structure. Fixed-effects model (inverse variance) was employed. Four studies with a total of 308 subjects were included in meta-analysis. One hundred twenty-five subjects were in group A; 183 subjects were in group B. Mean age in group A was 62,1 years, whereas in group B 59,9 years. The highest risk of bias regarded "comparability" domain, whereas the lowest pertained to "selection" domain. The mean relative risk of HRVA in group A (RA) as compared with group B (non-RA) was as follows: RR = 2,11 (95% CI 1,47–3,05), $I^2 = 15{,}19\%$, Cochrane Q = 3,54 with overall estimate significance of $p < 0{,}001$. Rheumatoid arthritis is associated with over twofold risk of developing HRVA, and therefore, vertebral arteries should be meticulously examined preoperatively before performing craniocervical fusion in every RA patient.

Keywords High-riding vertebral artery · Craniocervical fusion · Atlantoaxial dislocation · Atlantooccipital dislocation · Meta-analysis · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease affecting synovial joints as well as other organs with high morbidity and increased mortality [6]. Among many skeletal regions, cervical spine is also often disturbed possibly resulting in atlantoaxial instability [19]. However, little has been written about the immediate surroundings of the vertebral artery at the level of C2 in RA patients (Fig. 1). Mainly, its anomalies are rather congenital than acquired [20]. However, recent data suggests that one of its variants, namely high-riding vertebral artery, might be more common in patients with RA [8]. High-riding vertebral artery (HRVA) is defined as internal height of C2 ≤ 2 mm and/or C2 isthmus height ≤ 5 mm measured at the level 3 mm lateral to the border of spinal canal [16]. Identification of HRVA is crucial before approaching craniocervical junction fusion, as it determines a surgical method [8]. Modality of imaging used to diagnose HRVA is usually computed tomography angiograms (CTA). The overall prevalence of HRVA in general population is 25,3% [8]. It is speculated that in RA it might be higher, approximately 42,9% [8]. The literature, though, is not unanimous, with some papers stating to the contrary [10], and relative risk (RR) has not been estimated yet. Therefore, a timely meta-analysis appears to be contributory. To the best of our knowledge, this is the first attempt in the literature to provide RR of HRVA for patients with RA. The null

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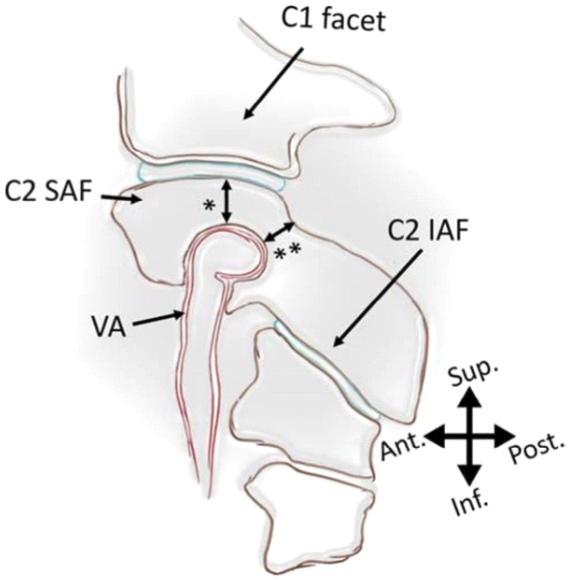

Fig. 1 Sagittal section of atlantoaxial facetal joint. High-riding vertebral artery is defined as isthmus height < 5 mm or/and internal C2 height < 2 mm measured at the level 3 mm lateral to the lateral border of spinal canal. SAF, superior articular facet. IAF, inferior articular facet. VA, vertebral artery. *Internal height. **Isthmus height. Ant., anterior. Post., posterior. Sup., superior. Inf., inferior

hypothesis is that the 95% confidence interval RR includes 1, meaning the risk is not increased for RA patients.

Methods

Search strategy

Two researchers (neurosurgical resident TK & JC) scanned the following databases: PubMed MEDLINE, Web of Science, EMBASE, SciELO, and China National Knowledge Infrastructure. Search terms included "rheumatoid arthritis" AND "high-riding vertebral artery," "high-riding vertebral groove," "axial isthmus," "high-riding transverse foramen," "C2 isthmus," "high-ride vertebral artery," "HRVA," "axis isthmus," and "vertebral artery." Time span was not restricted. The authors strictly followed MOOSE checklist (Electronic Supplementary Material 1). Titles were imported into Mendeley Desktop 1.19.4, which was also used for creation of the bibliographic data. Next, de-duplication was conducted. References of the included articles were tracked in order to identify any potentially missed papers.

Eligibility

The following inclusion criteria were imposed: (1) cohort studies with exposed and unexposed groups, (2) patients with rheumatoid arthritis as an exposed group, (3) subjects without rheumatoid arthritis as an unexposed group, (4) information on incidence of HRVA per person, and (5) Neo's and Bloch's definition of HRVA (internal height ≤ 2 mm and/or C2 isthmus height ≤ 5 mm measured at the level 3 mm lateral to the border of spinal canal). Of note, the above-mentioned measurements incorporated into the definition of the HRVA had to be taken in sagittal section of computed tomography (either classic or CTA). Exclusion criteria were determined as (1) groups who were operated on by means of unilateral C1-C2 transarticular fixation (in order to avoid a possible bias due to a high risk of unilateral HRVA), (2) papers with overlapping data, (3) case reports, (4) cohort studies with a total number of patients less than 10, (5) letters to the editors, (6) commentaries, (7) conference abstracts, (8) insufficient data, (9) no definition of HRVA, (10) reviews, (11) surveys, and (12) errata. English language was not a condition—articles in other languages were translated by proficient speakers of the given language and then evaluated by the authors. In order to avoid data overlap, studies of the same authors were given a particular attention so as to identify any overlapping recruitment timeline or inclusion criteria.

Data extraction

Two authors did the data extraction independently into the spreadsheet of Microsoft Excel 2016 (Redmond, USA). Pieces of information aimed to be extracted were as follows: (1) number of subjects without RA, (2) number of subjects with RA, (3) number of non-RA subjects with HRVA, (4) number of RA patients with HRVA, (5) geographical location, (6) age, and (7) sex. If an article was lacking important data, corresponding authors were communicated with.

Risk of bias assessment

Quality check and risk of bias assessment of the studies included in this meta-analysis were conducted by means of Newcastle-Ottawa Scale (NOS) as well as by evaluation of the funnel plot symmetry. Two researchers (neurosurgical resident TK & JC) assessed each of the included studies separately. In case of discrepancy, a senior neurosurgeon (LS) was called in so as to reach consensus. All articles were evaluated based on three domains: (1) selection, (2) comparability, and (3) outcome. A maximum of stars that could have been awarded for each domain was as follows: for "selection" four stars, for "comparability" two stars, and for "outcome" three stars. Lack of any stars in a given domain meant the risk of bias was high. At least one star but shy of a maximum meant the risk of bias of moderate. A maximum number of stars meant the risk of bias was low. For the sake of "outcome" domain in NOS, an adequate period of the established diagnosis of RA was arbitrarily set to at least 2 years.

Statistics

Meta-analysis was conducted by means of MetaXL 5.3, EpiGear International Pty Ltd. (Brisbane, Australia) and Statistica 13.3.0, TIBCO Software Inc. (Palo Alto, CA, USA). Relative risk (risk ratio; RR) was calculated with corresponding confidence interval of 95%. Heterogeneity was assessed based on I^2 and chi^2. I^2 value was interpreted with general accordance: 0 to 40%, not important; 30 to 60%, moderate heterogeneity; 50 to 90%, substantial heterogeneity; and 75 to 100%, considerable heterogeneity. Level of significance for Cochrane Q p value was arbitrarily set to < 10% (< 0,10). Level of significance for p value of comparative tests was arbitrarily set to < 5% (< 0,05). For heterogeneity lower than 40%, fixed-effects model was planned. In case of heterogeneity ≥ 40%, random-effects model would be adapted.

Results

Selection process and study characteristics

A flow diagram shows steps of the selection process (Fig. 2). Of 346 studies yielded by the initial search (344 from search engines, 2 from relevant references), 193 left once deduplication process was completed. One hundred eighty-four records are eliminated at the level of title and abstract screening (182 from the search engines, along with 2 articles that were found through references—exclusionary reasons are shown in Fig. 2). Nine full-text articles were assessed for eligibility criteria. Finally, 4 studies were deemed eligible for meta-analysis comprising a total of 308 subjects. One hundred twenty five were in group A (the exposed arm of RA patients), whereas 183 were in group B (the unexposed arm of non-RA subjects) [4, 5, 10, 15]. One study [14] was included in qualitative, but not in quantitative synthesis due to an unacceptable risk of bias; therefore, it is addressed separately in discussion. Mean age in group A was 62,1 years, whereas in group B 59,9 years. All four studies were of Asian origin. Details are presented in Table 1.

Risk of bias and quality assessment

Summary of the Newcastle-Ottawa Scale for each study included in the meta-analysis is shown in Table 2. In "selection" and "outcome" domains, all studies presented a moderate risk of bias. On the other hand, within the "comparability" domain, most of the studies presented a high risk of bias. Demonstration that outcome of interest (HRVA) was not present at the beginning of the studies was not feasible as it would have required CT scans prior to establishing diagnosis of RA. The funnel plot (Fig. 3) indicates that quantitatively only one study [10] strongly deviated from the rest, yet it had the least impact upon the mean RR.

Estimated pooled effect

The combined relative risk estimate was RR = 2,11 (95% CI 1,47–3,05), I^2 = 15,19%, Cochrane Q = 3,54, p = 0,32. Test for overall effect was significant with p < 0,001. The forest plot indicates mean distribution of RR across the studies along with the pooled effect (Fig. 4).

Discussion

Although several papers indicated that RA might pose a risk of developing HRVA, some small studies stated to the contrary. In a small study of Lee J et al., none of three RA patients had HRVA [10]. Their study had little impact upon the overall pooled estimate, though. Studies of larger samples and lower risk of bias state that HRVA are clearly more common in RA patients. This meta-analysis confirms that, according to the current data, the relative risk is increased approximately twofold.

Presumed pathophysiology explaining the findings

Findings of this meta-analysis might be elucidated by progressive reduction of volumetric bone mineral density [18]. RA is known to induce osteoporosis in multiple ways [11]. It might be either systemic, periarticular, or focal. Thinning of the

Table 1 Characteristics of the included studies

Study name	Total cases	RA	RA with HRVA (%)	Non-RA	Non-RA with HRVA (%)
Chung 2005	67	16	10 (62,5%)	51	17 (33,3%)
Higashino 2009	129	90	31 (34,4%)	39	3 (7,7%)
Lee J 2007	12	3	0 (0%)	9	3 (33,3%)
Moon 2018	100	16	9 (56,3%)	84	22 (26,2%)

RA patients with rheumatoid arthritis. *HRVA* high-riding vertebral artery

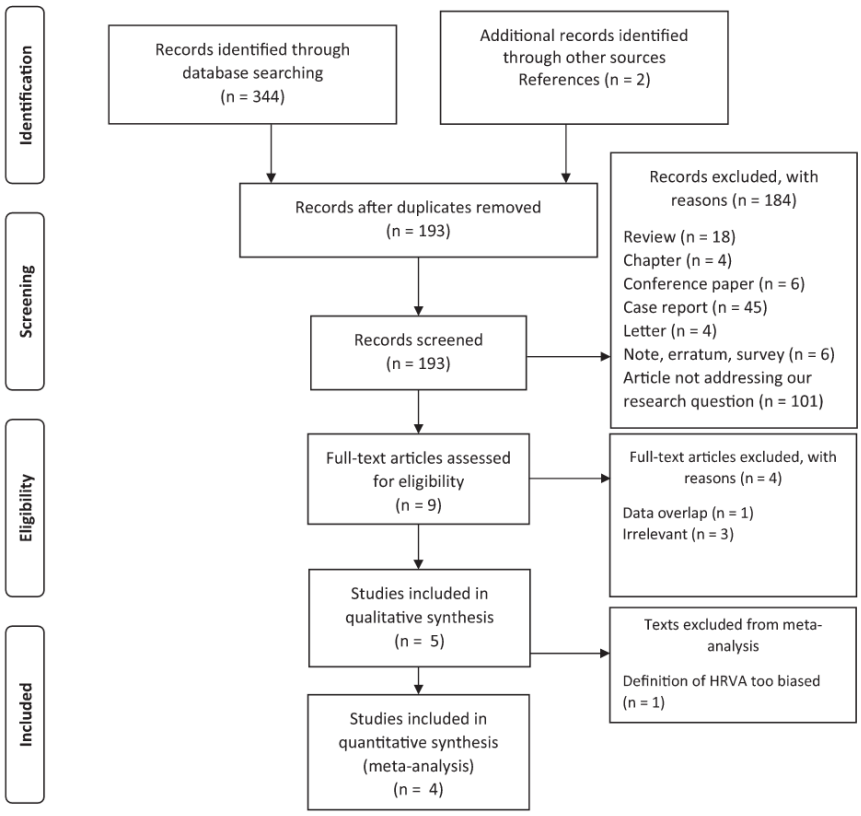

Fig. 2 A flow diagram depicting the study selection process

isthmus appears to combine all these three types of osteoporosis. Periarticularly, there is significant loss of trabeculae in number and in size stemming from prolonged secretion of pro-inflammatory cytokines, such as tumor-necrosis factor and interleukin 6. Systemically, disturbed osteoblastogenesis and enhanced osteoclastogenesis lead to generalized resorption of both cortical and trabecular bone. Locally, weak and demineralized bone of C2 vertebra, with transverse foramen located close to the superior articular facet, is being constantly thrusted into by the pulsating VA, over time creating a local effect of furrowing. This erodes the isthmus, rendering it insufficient in terms of screw placement. Evident cervical erosions in conventional radiographs are noticed in 16% of RA patients at 9-year follow-up [2] but much more often in CT scans [8].

Table 2 Tabular display of the Newcastle-Ottawa Scale summarizing qualitative evaluation of the risk of bias

Study name	Selection	Comparability	Outcome
Chung 2005	✱✱		✱✱
Higashino 2009	✱✱✱	✱	✱✱
Lee J 2007	✱		✱
Moon 2018	✱✱		✱

A maximum number of stars that could be awarded was as follows: four for selection, two for comparability, three for outcome

Craniocervical fusion in RA patients

Rheumatoid patients' atlantoaxial joints are prone to inflammation, subluxation, and dislocation [13, 21]. Formation of pannus around the dens of C2 as well as dens invagination into the foramen magnum might lead to craniocervical stenosis and subsequently to myelopathy of the bulbospinal junction. Many approaches are available for dens pathologies in rheumatoid arthritis including transoral release or extreme lateral [1]. Currently, treatment shifts from transoral release and posterior fusion toward solely posterior fusion, as it has been proven that craniocervical fixation leads to pannus resolution at follow-up visits [9]. As craniocervical dislocation in RA patients is often precipitated by trauma, its management shares some similarities with post-traumatic patients: for both, levels of fusion are most often C1-C2, followed by occiput-C2 [3, 7]. Precise insertion of the screws is of a paramount importance. Failure to notice a high-riding vertebral artery preoperatively

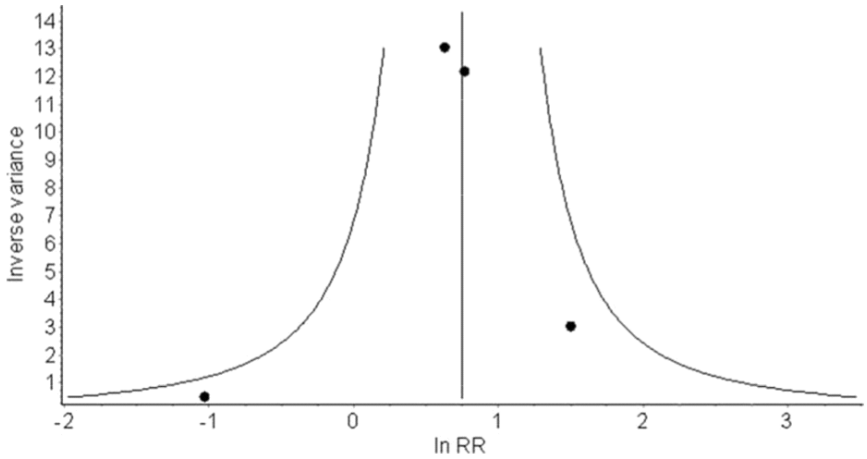

Fig. 3 A funnel plot illustrating quantitative assessment of the risk of bias

at the planning stage may lead to choosing a risky method of craniocervical fusion, ultimately ending up in injuring the VA, massive blood loss, and neurological deficits. Recently, a detailed guide for clinical decision-making was provided, which facilitates choice of fusion method depending on the side of dominance of VA and whether HRVA is unilateral or bilateral [8]. In ipsilateral HRVA and dominant VA, it is recommended to either avoid transarticular/transpedicular screw or proceed only with spinal navigation.

Limitations

A small number of studies are a limitation of the present meta-analysis. One potentially contributory cohort study of Miyata et al. [14] had to be rejected from quantitative meta-analysis at the level of eligibility evaluation due to imprecise definition of HRVA, as it would have possibly introduced an unacceptable risk of bias ("the maximum screw diameter that could be inserted through the isthmus of the axis without breaching the cortex"). This peculiar definition was followed by oddly high incidence of HRVA (70,2% in RA vs 15% in non-RA); therefore, the authors of the present meta-analysis decided not to include it quantitatively but only consider it in qualitative pondering. Regional differences in HRVA definition are prominent. For instance, Paramore et al. [17] from North America named vertebral arteries high-riding if the transverse foramen was on the path of ideal transarticular screw trajectory. As useful as it might appear in day-to-day clinical practice, it is not optimal for comparative research studies due to lack of standardization. European studies are also not unanimous. Meyer et al. [12] listed 7 patients with HRVA but did not provide any definition of it, whereas Czech study of Vaněk et al. [20] adhered to the Asian definition (internal height ≤ 2 mm and/or C2 isthmus height ≤ 5 mm measured at the level 3 mm lateral to the border of spinal canal). Besides, among other limitations, all four studies coming from Asia may question validity of the results in other populations. Therefore, more studies in the future are necessary exploring relationship between rheumatoid arthritis and high-riding vertebral artery in the remaining continents. Acknowledging this issue, the authors of this meta-analysis have commenced a CT-based cohort study on HRVA of the East European population. Moreover, it is worth mentioning that 2 of the studies had relatively wide range of 95% CI, putting significant weight of the pooled RR into the other 2 studies with narrow 95% CI (Fig. 4). This weakens the findings of the meta-analysis highlighting the need for more studies. Additionally, as shown in the tabular display of NOS (Table 2), the currently available data, although the best we have now, is flawed with methodological bias, especially in terms of comparability.

Conclusion

Rheumatoid arthritis is associated with an increased risk (RR = 2,11 [95% CI 1,47–3,05]) of developing a high-riding

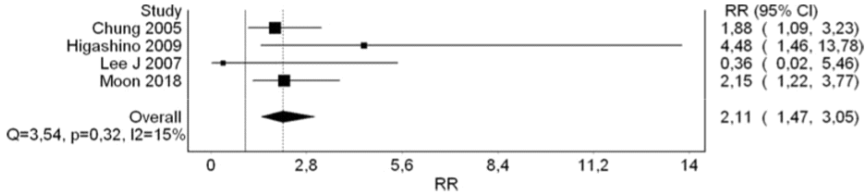

Fig. 4 A forest plot of the analyzed studies indicating that rheumatoid arthritis is a risk factor for high-riding vertebral artery

vertebral artery. Therefore, VAs should be thoroughly examined on CT angiograms before performing craniocervical fusion in these patients. The presence of HRVA might influence choice of approach. More research studies with better methodology encompassing subjects outside Asia are needed in order to extrapolate the results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval For this kind of study no ethics approval was required.

Consent to participate As this was a retrospective analysis of the studies that had been published in the past, no consent to participate was necessary.

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REVIEW

Management of post-traumatic craniovertebral junction dislocation: A PRISMA-compliant systematic review and meta-analysis of case reports

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Abstract
Although historically considered fatal, with the advent of improved pre-hospital care, traumatic dislocation of the craniovertebral junction (CVJ) has been increasing in prevalence in neurosurgical centers. As more survivors are reported each year, a timely review with meta-analysis of their management seems necessary. PRISMA checklist was followed step by step. PubMed and Web of Science databases were searched using words "craniovertebral junction dislocation" and their corresponding synonyms. Study eligibility criteria included research studies from 2015 onwards that delineated adult and pediatric patients with confirmed post-traumatic atlantooccipital dislocation (AOD) or atlantoaxial dislocation (AAD) who survived until proper treatment. Of 1475 initial records, 46 articles met eligibility criteria with a total of 141 patients with traumatic CVJ dislocation. Of the patients, 90 were male (63.8%). Mean age of the cohort was 33.3 years (range 1–99 years). Trauma that most often led to this injury was road traffic accident (70.9%) followed by falls (24.6%). The majority of authors support posterior instrumentation of C1-C2 (45.2%) especially by means of Goel-Harms method. At mean follow-up of 15.4 months (range 0.5–60 months), 27.2% of treated patients remained neurologically intact. Of initially symptomatic, 59% improved, 37% were stable, and 4% deteriorated. Instrumenting the occiput in cases of pure AAD was associated with lower chance of neurological improvement in chi-square test ($p = 0.0013$) as well as in multiple linear regression ($\beta = -0.3$; $p = 0.023$). The Goel-Harms C1-C2 fusion is currently the most frequently employed treatment. Many survivors remain with no deficits or improve, rarely deteriorate. Involving the occiput in stabilization in cases of AAD without AOD might be related with worse neurological prognosis.

Keywords Craniovertebral junction dislocation · Trauma · Atlantoaxial joint · Atlantooccipital joint

Introduction

Craniovertebral junction (CVJ) is a term encompassing occipitoatlantal and atlantoaxial complex of joints and ligaments. The former of the joints is said to provide stability, whereas the latter is responsible for the wide range of motion, accounting for more than half of the cervical spine rotation [1–3]. Dislocation of the junction happens when the integrity of the articular capsule is breached and might occur at each of the joints. Furthermore, it may be of congenital, inflammatory, or traumatic etiology. Traumatic dislocation of craniovertebral junction, although once considered fatal, has been proven numerous times that it can be a survivable injury [4]. It is mainly due to improvement made in the pre-hospital stage of care. Therefore, more and more survivors are encountered who require proper stabilization, which can be either conservative or surgical. Traumatic atlantooccipital dislocation (AOD) constitutes 1% of all injuries to the cervical spine and is believed to be less common than traumatic atlantoaxial dislocation (AAD) which constitutes 2.7% [5].

Rationalizing the study, we found no systematic review on the post-traumatic CVJ dislocation. Hence, considering recent advances in resuscitation, radiological diagnostic tools, and increasing choice of neurosurgical options, a timely review seems necessary. Utilizing the structured guidelines of the

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PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group has become a standard for high-quality review studies. As proven by Sampayo-Cordero et al. in 2018 [6], a meta-analysis of case reports is accurate and agrees with a meta-analysis of clinical randomized studies and is dedicated for rare diseases that often times have zero events in either both arms. Since adequate records of post-traumatic CVJ are reported solely in case reports or case series, a meta-analysis based on case reports is well rationalized. This study aims to answer questions of what state-of-the-art treatment patients with traumatic dislocation of CVJ are currently receiving, what outcomes they are likely to obtain, and whether plating the occiput affects patients' outcome.

Materials and methods

PRISMA checklist was followed step by step (Electronic Supplementary Material No. 1). Participants, interventions, context, outcome, and study designs are shown in Table 1. On 17 February 2020, two databases, PubMed Medline and Web of Science, were perused using search words "craniovertebral junction dislocation" and their corresponding synonyms. Full electronic search strategy can be found here (Electronic Supplementary Material No. 2).

Eligibility criteria included latest research studies from 2015 to 2020 that delineated patients with post-traumatic craniovertebral junction dislocation. We defined dislocation as a ligamentous injury with ensuing misalignment of the facets. Thus, what was searched was radiological evidence of either obvious loss of facetal contact or positive testing for classic radiological markers. Concomitant lesions or fractures within the CVJ were acceptable as long as post-traumatic facetal misalignment was present. Inclusion and exclusion criteria are shown in Table 2. Extraction of the data from the gathered reports was conducted by the first author (TK) and then independently checked and confirmed by the co-authors (BL and LS) so as to ensure minimal risk of bias of individual studies. Collected variables included number of traumatic cases in a given publication, patients' sex, age, mechanism of trauma, resultant injury, underlying disease (if present), therapeutic interventions, levels of fusion, surgical technique, and outcomes (subjective pain analysis, neurological assessment, fusion rates) at a specified follow-up period. Conservative treatment information was retrieved only when there was no subsequent surgery. If a patient received both conservative and surgical management, focus was on the latter. Pain relief as an outcome was noted only if there was pain at presentation. Thus, a documented change in pain intensity after treatment was searched for extraction. Neurological status was assessed both preoperatively and postoperatively and tendency was written down. Accepted forms of neurological status assessment were as follows: quantified scores of myelopathic grading systems such as Japanese Orthopedic Association (JOA) score, its modified variant (mJOA), American Spinal Injury Association (ASIA) score, Nurick score, as well as authors' subjective examination. Due to lack of unified neurological assessment methods among the authors, gross tendencies were grouped into the following categories: remained intact, improved, stable, and deteriorated. Additionally, fusion rates were collected—fusion was defined as documented lack of movement of the stabilized joints assessed on lateral X-ray. Subjective authors' statement of solid fusion was acceptable. Although subjectivity adds a risk of bias, we assumed that proper radiological assessment had been done in order to declare fusion. No funding was expected at the beginning of the study and none was obtained throughout the process. Statistical analysis of the data was performed by means of Statistica 13 (TIBCO Software Inc.). Pearson's chi-square test would be used for categorical variables, whereas continuous variables would be computed by Wilcoxon-Mann-Whitney or Kruskal-Wallis test. Multiple linear regression was used to assess relations between neurological change at follow-up (dependent variable) and sex, age, type of dislocation, and plating the occiput (independent variables).

Results

The PRISMA flow diagram shows steps of the inclusion process (Fig. 1). Initial search presented 1475 titles. Having

Table 1 PICOS acronym describing characteristics of this review study

Acronym	Definition	This study
P	Participants	Children and adults with post-traumatic AOD, AAD, or both who survived until treatment
I	Intervention	Anterior or posterior reduction and instrumentation with levels of fusion and status of occipital involvement. If there was no surgery, conservative management details of traction and bracing would be presented
C	Context	Trauma—its mechanism as well as basic demographic data of patients
O	Outcome	Neck pain, NDI, JOA, mJOA, Nurick scale, ASIA, subjective improvement, fusion rates
S	Study designs	Cross-sectional and longitudinal cohort studies, case series ($n \geq 3$), case reports ($n \leq 2$)

AAD, atlantoaxial dislocation; AOD, atlantooccipital dislocation; ASIA, American Spinal Injury Association Impairment Scale; mJOA, modified Japanese Orthopedic Association score; NDI, neck disability index

Table 2 Inclusion and exclusion criteria for the studies screened and checked for eligibility

Inclusion criteria	Exclusion criteria
1. Publications from 2015 to 2020	1. Reoperations
2. Dislocation of atlantooccipital or atlantoaxial joints	2. Commentaries
3. Trauma as the primary cause (underlying diseases and fractures are acceptable)	3. Review articles
4. Adequate records for evaluation	4. Radiological articles
5. Full text available in English or Polish	5. Insufficient medical history
6. Treatment method listed	6. Cadaveric or animal studies
	7. Subject died before treatment was employed
	8. Dislocation due to non-traumatic causes (congenital, inflammatory, syndromic)

removed duplicates, 894 titles and abstracts were collected for screening (Table 3). A total of 46 full-text articles were deemed eligible for inclusion [3, 7–50]. The highest level of evidence of the included papers was IV. They comprised 141 cases, 90 of which were male (63.8%), 46 were female (32.6%), and gender of 5 patients was not stated. Mean age of the cohort was 39.2 years (range 8 months to 99 years). For adults mean age was 46.7 years (range 19–99 years). On the other hand, in the pediatric subpopulation, mean age was 4.9 years (range 8 months to 17 years). Mechanism of injury was known in 110 patients (78.0%). Among them, the most common trauma was road traffic accident ($n = 78$) accounting for more than two-thirds of the cases (70.9%). Falls were the second leading cause of the traumatic CVJ dislocation constituting nearly a quarter of cases (24.6%). Occasionally, jumping headfirst into the water, assault, epileptic seizure, or being hit by a falling object might also lead to this condition (altogether 4.5%). Diagnosis in majority of cases was atlantoaxial dislocation (62.4%, $n = 88$), followed by atlantooccipital dislocation (27.7%, $n = 39$) and combined AAD with AOD (9.9%, $n = 14$). Most authors go for surgical management even if initial nonoperative reduction was achieved. In total, 95.7% ($n = 135$) were operated on at some point, either as a primary treatment option or as a result of

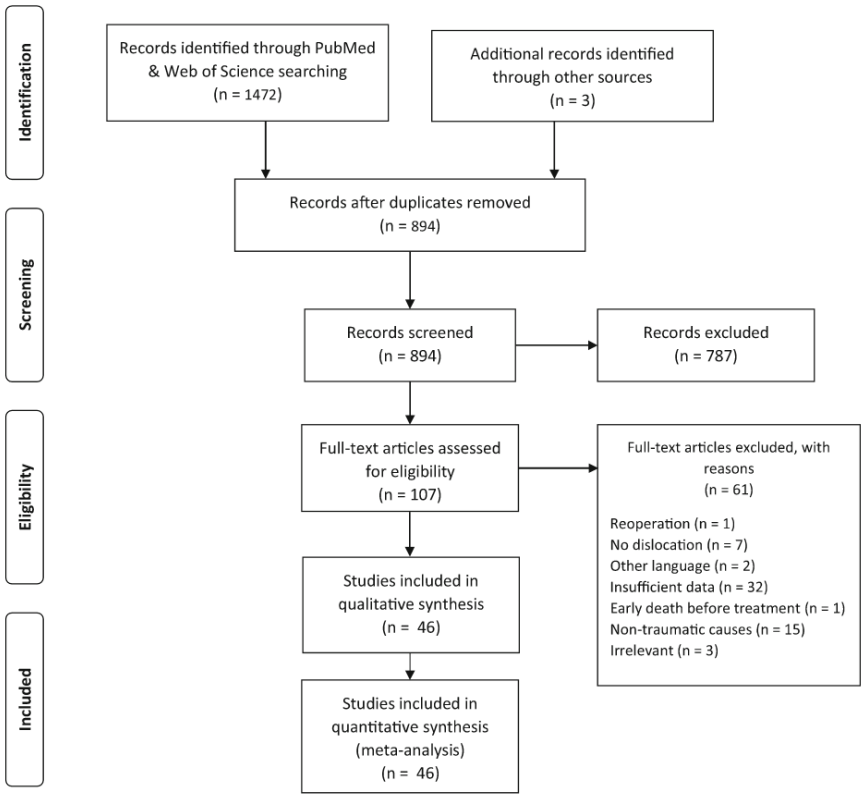

Fig. 1 A flow diagram depicting the process of including studies into the review and meta-analysis

Table 3 Summarized reviewed studies

Authors	Year	Cases (M/F)	Mean age (years)	Injury (*n*)	Diagnosis and concomitant anomalies (*n*)	C or S[a]	Fusion level	Technique	Mean FU (mo)	Outcome[b] [% of patients in the series]
Grover [7]	2020	5 (3/2)	1,8	N/A	AAD; OF A-D II (3), OO (1)	S	C1-C2 (4), O-C3 (1)	SLW (4) + OP (1)	14.4	20% improved; 80% stable; 100% fusion rate
Singla [8]	2020	1 (1/0)	25	RTA	AAD rotatory Fielding I	S	C1-C2	LM-P	N/A	100% remained intact and NP reduced
Barimani [9]	2019	1 (0/1)	66	Ritual	AAD rotatory Fielding II	S	C1-C2	LM-P	3	100% remained intact and NP reduced
Biakto [10]	2019	1 (1/0)	17	RTA	AAD anterior; OF A-D II; C1 Gehweiler II	S	O-C4	OP-LM-P	2	100% improved and NP reduced
Ghailane [11]	2019	1 (1/0)	89	Fall	AAD posterior	C	None	Close reduction + rigid collar for 2 mo	8	100% remained intact and NP reduced
Garcia-Pallero [12]	2019	1 (0/1)	28	RTA	AAD rotatory	C	Nonoperative	Traction + rigid collar for 16 w	48	100% NP reduced
Tavolaro [13]	2019	2 (2/0)	44	RTA (2)	AAD (2): posterior (1), anterior (1); JF (2); OC-C1 (1); atlas assimilation (2)	S	O-C6 (1), C1-C3 (1)	OP-TLS-LM (1); LM-P (1)	N/A	50% improved; 50% deteriorated and died
Meyer [14]	2019	9 (3/6)	57,1	RTA (3), fall (6)	AAD (9), OF A-D II (5), III (1)	S	C1-C2 (7), O-C-Th or O-C (2)	LM-P (7)	N/A	N/A
Musa [15]	2019	1 (1/0)	87	Fall	AAD lateral, OF A-D II	S	C1-C2	LM-P	18	100% NP reduced; 100% fusion rate
Keen [16]	2019	15 (7/-8)	3,8	RTA (15)	AOD (10), AAD (10)	S	O-C2 (12), O-C3 (2), O-C4 (1)	OP-TLS-SLW (12) + LM (3)	33	53.3% remained intact; 26.7% improved; 20% stable 100% fusion rate
Park [17]	2019	1 (0/1)	21	Fall	AAD and AOD vertical	S	O-C4	OP-LM-P	12	100% stable; 100% fusion rate
Zitouna [18]	2019	1 (1/0)	74	Fall	AAD rotatory Fielding III, OF A-D II	S	O-C2	OP-LM	N/A	100% deteriorated and stable NP
Suzuki [19]	2018	1 (0/1)	87	Fall	AOD vertical; OCF A-M I, Tuli I (1)	S	O-C2	OP-P	N/A	100% remained intact
Minyu [20]	2018	1 (1/0)	30	RTA	AAD posterolateral; OF A-D II	S	C1-C2	LM-P	60	100% remained intact and NP reduced; 100% fusion rate
Tobert [21]	2018	1 (1/0)	35	RTA	AOD vertical & AAD vertical	S	O-C4	OP-LM	12	100% remained intact; 100% fusion rate
Salunke [22]	2018	6 (6/0)	56	-	AAD posterior (6), OF A-D IIb	S	C1-C2 (6)	LM-P (6)	22	16.7% remained intact; 83.3% improved; 100% fusion rate
Ma [23]	2018	10 (6/-4)	50	N/A	AAD (10); OF (10)	S	C1-C2 (6), O-C2 (2), O-C3 (1), C1-C4 (1)	LM-P (7)	22.2	100% improved; 100% fusion rate
Abouelleil [24]	2018	1 (0/1)	19	RTA	AOD, AAD	S	O-C3	OP-LM-P	12	100% remained intact and NP reduced
Kumar [25]	2018	1 (1/0)	11	RTA	AAD (spondyloptosis), OF	S	C1-C2	LM-P	6	100% improved
Robles [26]	2018	1 (1/0)	67	Swimming	AOD rotatory, OCF type III	S	O-C1	N/A	4	100% remained intact and NP reduced
Anania [27]	2018	1 (1/0)	74	Fall	AOD incomplete, AAD anterior; OCF	S	O-C4	OP-LM-SLW-TAS	N/A	100% remained intact
Eghbal [28]	2018	1 (1/0)	21	RTA	AAD rotatory	S	C1-C2	LM-P	6	100% improved and NP reduced
Russo [29]	2017	1 (1/0)	22	RTA	AAD vertical, OCF type II, spinal hygroma	S	C1-C2	LM-TLS	12	100% improved; 100% fusion rate
Nowell [30]	2017	1 (1/0)	71	RTA	AAD posterior, bilateral VA occlusion, C1 Gehweiler I	S	C1-C2	LM-P	N/A	100% remained intact
Larsen [31]	2017	1 (0/1)	75	Fall	AAD rotatory	S	C1-C2	SLW-TLS	6	100% remained intact and NP reduced; 0% fusion
Wang [3]	2017	18 (15-/3)	39,2	RTA (11), fall (5) direct hit (2)	AAD (18); OF (13), JF (1), HF (4)	S	C1-C2 (12), OC (6)	N/A	15,3	52.94% improved; 47.06% stable; 83.3% fusion
Hale [32]	2017	1 (0/1)	1	RTA	AOD vertical; AAD vertical	S	O-C2	OP-LM-P	12	100% improved; 100% fusion rate
Eghbal [33]	2017	1 (1/0)	35	Fall	AAD rotatory Fielding I	S	C1-C2	LM-P	N/A	100% improved

Table 3 (continued)

Authors	Year	Cases (M/F)	Mean age (years)	Injury (*n*)	Diagnosis and concomitant anomalies (*n*)	C or S[a]	Fusion level	Technique	Mean FU (mo)	Outcome[b] [% of patients in the series]
Ivetic [34]	2017	1 (1/0)	54	Sports	AAD anterior	S	C1	LM-TLS	N/A	100% improved and NP reduced
Peyriere [35]	2017	5 (2/3)	60	RTA (1), fall (3), epilepsy (1)	AAD rotatory (5)	S	C1-C2 (2), C1-C3 (3),	LM-P (4), TAS (1)	12	80% remained intact, 20% stable; 100% NP reduced and fusion rate
He [36]	2016	1 (1/0)	72	Fall (1)	AAD posterolateral; OF A-D II	S	C1-C3	LM-P	12	100% stable and persistent NP; 100% fusion rate
Han [37]	2016	1 (0/1)	19	RTA	AAD rotatory; HF III	C	Nonoperative	Bidirectional traction for 3 w	3	100% stable and NP reduced
Ueda [38]	2016	1 (1/0)	57	Bicycle fall	AOD posterior; OCF, contusion of cerebellar hemisphere	S	O-C3	OP-LM-P	60	100% improved and NP reduced; 100% fusion rate
Dahdaleh [39]	2016	6 (4/2)	33,3	N/A	AOD (6), OCF (1), JF (1)	S	O-C2 (1), O-C3 (4), O-C4 (1)	OP-LM-P (6)	15,4	66.7% improved, 16.7% remained intact, 16.7% deteriorated and died
Walbom [40]	2016	1 (0/1)	6	Fall	AAD rotatory and displaced ossiculum terminale	C	Nonoperative	Halo traction for 21 w	26	100% improved and NP reduced
Beez [41]	2016	1 (1/0)	9	RTA	AOD	S	O-C3	OP-P	12	100% improved
Mendenhall [42]	2015	23 (14-/9)	36,9	RTA (23)	AOD (23): anterior (10), posterior (9), distractive (3)	S	O-C2 (7), C1-C2 (2), O-C3 (9), O-C4 (4), O-C5 (1)	N/A	3	21.74% improved, 73.91% stable; 4.35% deteriorated
Krishnan [43]	2015	1 (1/0)	10	Fall	AAD rotatory	S	C1-C2	LM-P	N/A	100% improved; pain stable
Salunke [44]	2015	6 (N/-A)	N/A	RTA (5), fall (1)	AAD anterior (5), posterior (1); OF (6)	S	C1-C2 (6)	LM-P (6)	14	33.3% remained intact; 66.6% improved; 100% NP reduced; 83.3% fusion rate
Hawi [45]	2015	1 (0/1)	34	RTA	AAD rotatory	C	Nonoperative	Halo traction 2 w, rigid collar 6 w	6	100% remained intact and NP reduced
Yang [46]	2015	1 (1/0)	70	RTA	AAD rotatory	C	Nonoperative	Traction, rigid collar 8 w	6	100% remained intact % NP reduced
Xu [47]	2015	1 (1/0)	54	RTA	AAD posterior F	S	C1-C2	AEO + LM-P	12	100% improved and NP reduced; 100% fusion rate
Hu [48]	2015	1 (1/0)	50	Fall	AAD posterior	S	C1-C2	TOO + LM-P	15	100% remained intact and NP reduced; 100% fusion rate
Salunke [49]	2015	4 (4/0)	41	N/A	AAD posterior (1), anterior (3)	S	C1-C2	LM-P	13	100% improved and NP reduced; 100% fusion rate
Chaudhary [50]	2015	1 (1/0)	26	RTA	AAD rotatory and HF L-E IIa	S	C1-C3	LM-P-SLW	16	100% remained intact; 100% fusion rate

[a] C for conservative treatment; S for surgical treatment

[b] Terms intact/improved/stable/deteriorated apply to neurological status

AEO, anterior endoscopic odontoidectomy; A-M, Anderson-Montesano classification; FU, follow-up; OO, os odontoideum; OF, odontoid fracture; OCF, occipital condyle fracture; w, weeks; mo, months; n, number of cases; NP, neck pain; SLW, sublaminar wire; OP, occipital plate; RTA, road traffic accident; TAS, transarticular screw; TLS, translaminar screw; LM, lateral mass screw; TOO, transoral odontoidectomy; JF, Jefferson fracture; N/A, not available or not specified

failed initial conservative management. Levels that were subject of fusion most frequently were as follows: C1-C2 (45.2%, $n = 61$), O-C2 (19.3%, $n = 26$), O-C3 (13.3%, $n = 18$), O-C4 (8.1%, $n = 11$), and C1-C3 (4.4%, $n = 6$). 8.1% of the treated ($n = 11$) were either unspecified or other levels (Fig. 2). For AOD the most common level of stabilization was O-C2 (35.9%, $n = 14$). Similarly for combined AOD with AAD, O-C2 was usually fused (57.1%, $n = 8$). Choice of level differed significantly for AAD and AOD ($p < 0.001$). 4.3% ($n = 6$) of all patients were treated conservatively with no subsequent surgery. All those nonoperative cases regarded atlantoaxial dislocation, but none atlantooccipital dislocation. This, however, was not statistically significant ($p = 0.129$, chi-square test). Neurological status prior to treatment was known in 97.2% ($n = 137$) of patients. Its quantification by means of JOA, mJOA, Nurick scale, or ASIA was done in 70 cases (49.6%). The remaining was authors' subjective examination. 27.2% ($n = 37$) were neurologically intact and remained so at follow-up, whereas 76.3% ($n = 100$) had neurological deficits on initial examination. Among the latter, 59% improved ($n = 59$), 37% were stable ($n = 37$), and 4% deteriorated ($n = 4$). Of all, 49.6% ($n = 70$) had their occipital bone involved in instrumentation. Within the group with initial neurological signs, patients without the occiput instrumentation were more likely to improve (48.1% vs 33.3%) and less likely to remain neurologically stable (9.3% vs 41.7%) ($p = 0.0013$, chi-square test; regards mainly pure AAD patients) at a mean follow-up of 15.4 months (range 0.5–60 months). Hindered improvement after plating the occiput was observed also in multiple linear regression model with the following dependent variables: mean age, sex, type of dislocation, and plating the occiput (Table 4). Debilitating neck pain was reported preoperatively by 43 patients (30.5%). Of those, at follow-up visit, neck pain improved in 36 patients (83.7%). Change in pain at a follow-up was not correlated with the status of occipital plating ($p = 0.4091$). Assessment of fusion rate was done in 81 survivors (57.4%). At follow-up visits, solid fusion was declared in 76 (93.8%).

Discussion

In this study, we touched upon several important aspects. As Winegar et al. in 2010 noted, neck pain improvement after treatment of dislocation of CVJ is generally highest in traumatic cohort [51]. They had detailed information on pain in 28 post-traumatic cases, and improvement after treatment was seen in 22 (78.57%). Our review gathered data on pain from 43 patients with improvement of 83.7% ($n = 36$), confirming a high rate of pain alleviation in this group. According to the literature, after cervical injury, over 60% of survivors experience pain within the first 6 h, over 90% after a day, and basically everyone after 3 days following the trauma [52]. Fortunately, as we presented, successful stabilization paired with further rehabilitation can mitigate it better than in cases of other CVJ abnormalities. Importantly, as Debernardi noticed, if neck pain and stiffness are mild to moderate, it is more likely to overlook the diagnosis [53].

Atlantooccipital joint is regarded as the most stable joint of the body, whereas atlantoaxial joint as the most mobile one [1, 54]. Mobility of the latter, however, is the source of its susceptibility to dislocation. Hence, most cases of the CVJ dislocation happen at the atlantoaxial level. Atul Goel is convinced that majority of AAD do not require involvement of the occiput because there is no concurrent AOD [55]. He states that primary AAD needs only segmental fixation. Extensive multiple-level stabilization compromises the strength of the fusion. In addition, immobilization of both crucial units considerably reduces range of motion. Nevertheless, we showed that 18.2% of patients with pure AAD ($n = 16$) had occipitocervical stabilization. This might be even of higher importance considering the fact that in the presented analysis, involvement of the occipital bone was associated with lower chance of neurological improvement and higher risk of neurological stagnation, especially in cases of pure AAD without AOD. These findings, however, require confirmation in larger prospective studies. Authors of this review generally accept Goel's attitude that occipitocervical fusion is appropriate and

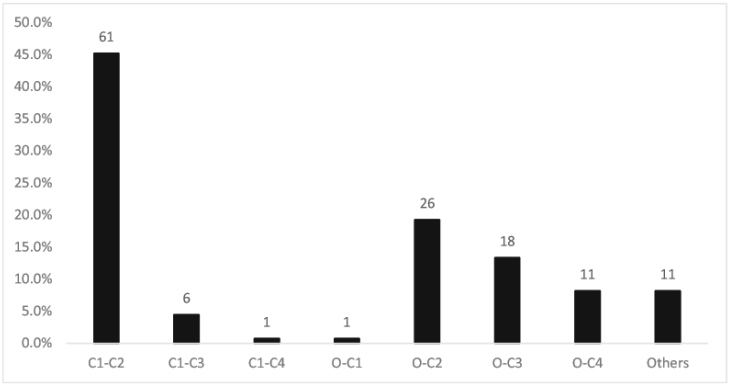

Fig. 2 A graph showing levels of instrumentation that were addressed most frequently. A number of patients with fusion at a given level are shown above the bars

Table 4 Multiple linear regression model to determine factors associated with neurological status at follow-up visits in patients with craniovertebral junction dislocation

	Neurological status at follow-up	
Variable	*β*	*p*
Age at operation	− 0.08	0.514
Sex (F/M)	0.19	0.120
Type of dislocation (AOD/AAD)	0.12	0.307
Plating the occiput (no/yes)	− 0.30	*0.023*

indicated in confirmed atlantooccipital dislocation. Good radiological markers for combined AAD and AOD facilitating decision-making seem to be basion-dental interval (BDI), revised C1-condyle interval (rCCI), and basion-axial interval (BAI) [56]. Especially rCCI with cut-off value of 2.5 mm has high sensitivity and specificity [56].

Our analysis revealed that a method of fusion which was chosen most often was Goel-Harms technique. C1-C2 segment was targeted in 61 patients. Of them, 49 had their construct details reported. Thirty-seven patients (75.5%) had implanted screws/rod construct in accordance with Goel-Harms approach. Rarely did authors from the selected studies choose wiring, and if so, it was mostly in children. From historical perspective, wiring was among the first of techniques introduced to the CVJ battlefield. Although wiring has shortest time to fusion, its failure rate is higher than that of Goel-Harms' rod-screw construct passing through the lateral masses of C1 and the pedicles of C2 [51].

In 1994, Goel introduced a concept of placing screws into both C1 lateral masses and C2 pedicles [57]. His initial idea back then was to put it monocortically. It was not until 2001 when Harms published his work stressing that bicortical purchase was desired [58]. Harms improved Goel's approach by applying polyaxial screws bicortically which provided stability for fully loaded rod connection. Goel-Harms C1-C2 fixation has several advantages over the classic Magerl's transarticular technique. First of all, it does not sacrifice the facets of the first two vertebrae. Omitting disruption of the capsule renders it potentially reversible which might save the range of motion after removal of the construct once the fracture has healed. Also, an angle required to perform the Goel-Harms stabilization is significantly easier to achieve since it is only ~ 22 degrees cephalad when compared with ~ 50 degrees of the Magerl [59–61]. Finally, the Goel-Harms procedure provides a way for one-stage open reduction of the dislocation and fusion utilizing the same anesthesia period and the same positioning [49, 61].

In this paper, sixteen patients (12.4% of the operatively treated) had translaminar screws implanted. This concept was introduced in 2004 by Wright [62]. One of the conditions that needs to be met is transverse diameter of the lamina larger than 3.5 mm [63]. Moreover, C1 lateral mass-C2 laminar method is inferior to Goel-Harms in terms of the stability during lateral bending and axial rotation [64]. It also poses a higher risk of damaging the spinal cord [65]. Additionally, from biomechanical point of view, it is not suitable for longer subaxial constructions when concomitant instabilities are present. However, it can be considered a rescue procedure in situations when C2 pedicle screws cannot be used.

Recently, new techniques began to emerge such as anterior transcervical or transnasal endoscopic odontoidectomy with reduction of the dislocation [47, 66, 67]. There was one such a case in our review. Notably, it is helpful in posterior atlantoaxial dislocation without associated dental fracture when the dens moves anteriorly and is challenging to reduce otherwise. Odontoidectomy might also be performed in a scarless fashion. These are, however, limited options for traumatic patients because of frequent concomitant nasofacial injuries as the most common mechanism of CVJ dislocation is still high-speed road traffic accident.

Our review sheds light upon the lack of unison in terms of methodology of reporting traumatic craniocervical junction sequelae. Too many potentially contributory papers had to be excluded because of insufficient data. Post-traumatic patients are often not distinguished from the reported cohort because of their relatively small number. It is understood that merging etiologies of the CVJ dislocation produces larger series, but it is at a cost of heterogeneity. One solution to this might be providing more details on the subgroups within the mixed series. Furthermore, for case reports as well as case series, it is recommended to furnish detailed and quantified neurological examination done prior to surgery and thereafter. Additional assessment at a distant follow-up would also be of high informative value. Obviously, for part of post-traumatic patients, preoperative evaluation is very challenging due to their poor general state. Those with delayed presentation, however, could be examined thoroughly with at least one of the following scales: mJOA, JOA, ASIA, or Nurick.

Limitations

First limitation of this research is absence of evidence stronger than level IV. Most authors report their cases in small series, rarely with any control group. Therefore, a meta-analysis based entirely on case reports/case series was carried out. This might bias the scientific truth because there is a tendency to present rather positive outcomes in case reports. Another restraint might be a scope of years of the included papers. We believe, however, that some relevant progress had been made

in the field of resuscitation, diagnostic tools, and neurosurgical management of the craniovertebral junction dislocation; therefore, only new publications from the last half a decade were accepted. Finally, lack of unanimous agreement on the manner in which outcomes are reported renders the outcome variable categorical rather than continuous.

Conclusion

Traumatic dislocation of CVJ is no longer equivalent to death. Due to advances in pre-hospital care, it has become a survivable injury. In-hospital management of choice is timely reduction, at first close with monitoring the patient's status. In case of irreducible dislocation, open reduction is mandatory with subsequent stabilization. For atlantoaxial dislocation with no other abnormalities of the cervical vertebrae, posterior C1-C2 fusion with the Goel-Harms method is the most appreciated approach, currently regarded as the gold standard. For atlantooccipital dislocation, occipitocervical instrumentation yields satisfactory results. For combined AAD and AOD, superior extension for Goel-Harms technique towards the occiput by means of occipital plating is recommended. Many survivors remain with no deficits or improve, rarely deteriorate. Involving the occiput, especially for pure AAD, might be related with hindered neurological improvement.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required.

Consent to participate As this was a retrospective analysis of the studies that had been published in the past, no consent to participate was necessary.

Consent for publication The authors of this study grant the Publisher the sole and exclusive license of the full copyright.

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13.5 Przedruk publikacji 5

Original Article

EuroQol-5 dimensions health-related quality of life questionnaire in craniovertebral instability treated with posterior fixation with or without occipital plating: A comparative study with matched datasets

ABSTRACT

Objective: Health-related quality of life (HRQoL) in craniocervical instability (CCI) before and after posterior fixation is yet to be determined. This study aimed to deliver novel and clinically relevant data about HRQoL (baseline, at follow-up, predictors, and correlates) in subjects with CCI treated with posterior fixation with or without occipital plating, and to compare it with matched datasets.

Methods: EuroQol-5 dimensions (EQ-5D) questionnaires were collected to evaluate HRQoL before surgery and at follow-up. Study sample size was estimated at 58. Comparison with representative datasets was done by matching on a many-to-many basis. Classic CCI parameters were measured. Strengthening the Reporting of Observational Studies in Epidemiology was followed.

Results: Sixty subjects were included. The mean age was 37.2 years. The median follow-up for EQ-5D was 26.3 months with interquartile range (IQR) 10.8 to 47.3 months. The median preoperative score of the 3-level version of EQ-5D (EQ-5D-3L) was 0.254 (IQR = −0.025 to 0.504), whereas at follow-up, it increased to 0.779 (IQR = 0.387–0.864) which is still worse than the 25th percentile (0.894) of the age-matched population. Occipital plating (n = 35; 58.3%) did not influence HRQoL trajectory (P = 0.692). In multiple linear regression, HRQoL at follow-up was affected by the age (β = −0.004; P = 0.049) and length of hospitalization (β = −0.134; P = 0.010). Of radiologic measurements, preoperative Wackenheim line correlated with HRQoL at follow-up (rho = −0.432; P = 0 − 028).

Conclusions: HRQoL is significantly reduced in CCI. Although this can be improved with posterior fixation, it is still worse than the age-matched population. Occipital plating may not influence HRQoL. HRQoL of the elderly might not increase as much as of the younger subjects. The longer hospitalization, the worse HRQoL could be expected. Preoperative Wackenheim parameter could correlate with HRQoL at follow-up.

Keywords: Atlantoaxial fusion, atlantooccipital fusion, craniocervical fixation, EuroQol-5 dimensions-3L, health-related quality of life, occipital plating

INTRODUCTION

Craniovertebral junction is a durable complex of articulations and ligaments.[1] Its instability, however, is potentially lethal due to vicinity of the critical neurovascular structures.[2-4] If the prehospital stage is survived, it oftentimes requires reduction and instrumentation. In recent years, the most popular technique of CCJ stabilization has been C1 lateral mass-C2 pedicle screw fixation with bicortical purchase.[3] This procedure was first introduced by Atul Goel in 1994 and then further developed by Harms in 2001.[5,6] CCJ dislocation and instability are understood to affect patients' health-related

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quality of life (HRQoL),[7,8] but the quantification of this phenomenon is yet to be determined. Moreover, HRQoL after craniocervical fusion is also unknown.

Therefore, we aim to present the first study of both adults and pediatrics, which shall detect the baseline HRQoL before craniocervical fusion and at follow-up. Furthermore, since it has been a matter of debate whether inclusion of the occiput is necessary for the craniovertebral stabilization,[9] we decided to conduct a direct comparison (HRQoL in groups with versus without the occipital plating) to aid the debate. The secondary goal was to determine whether there are any clinical or radiologic predictors of the follow-up HRQoL, and to compare the results with comorbidity-matched and age-matched datasets.

METHODS

Study design

It is an observational study whose concept has been reviewed and approved by the Institutional Review Board (KB-0012/24/04/2020/Z). Patients undergoing posterior craniocervical junction fusion at the tertiary neurosurgical center due to CCI were reviewed for eligibility criteria. EuroQol-5 dimensions (EQ-5D) questionnaires were collected to determine HRQoL prior to surgery and at follow-up via structured phone interview or directly during an outpatient visit. Strengthening the Reporting of Observational Studies in Epidemiology checklist was followed to provide a structure of quality.

Sample size estimation

Pwr package in RStudio was used for the sample size calculation with "pwr.f2.test" function. Based on the background information from similar studies on HRQoL in rare cervical spine entities,[10,11] the effect size was set at 0.35. Accepting probability of type I error at 5% ($\alpha = 0.05$) and expecting type II error at 20% ($\beta = 0.2$) with theoretical power of the study set at typical 80%, and a possible dropout rate at 30%, the minimum sample size has been estimated at 57,149 subjects (rounded up to 58) in the study group for significance of the multiple linear regression model with one dependent and four independent predictor variables.

Patient selection

Eligibility was met if (1) a subject suffered from CCI, (2) CCI was treated with instrumentation using posterior approach, (3) C1-C2 segment was included in fusion (additional inclusion of the occiput and/or lower cervical spine were acceptable, and discrete analysis was planned in advance for those with the occiput plating), and (4) cause of CCJ dislocation or instability was known. Radiologic evaluation was addressed if both preoperative and postoperative computed tomography scans of sufficient quality were accessible. HRQoL was calculated if follow-up was available. Patients were excluded from the study if (1) CCI was treated conservatively without posterior instrumentation, (2) patients could not comprehend the meaning of the questionnaire, (3) CT scans were of poor quality and, therefore, not able to be reformatted into sagittal sections, and (4) there was prior instrumentation of the craniocervical junction. The control group for age-matching on a many-to-many basis was obtained from the representative national database published by Golicki *et al*.[12,13]

Data extraction

The following items were extracted: (1) age at the time of surgery, (2) sex, (3) date of the follow-up, (4) cause of craniocervical dislocation, (5) symptomatology upon admission and (6) upon discharge, (7) level of instrumentation, (8) hardware system, (9) occipital involvement in fusion, (10) telephone number, (11) blood loss (mL), (12) duration of the surgery (minutes), and (13) duration of the entire hospitalization (days).

Surgical procedure

Every patient was subject to C1-C2 fixation via lateral masses of C1 and pedicles of C2. Adjacent levels were fixed with respect to medical indications. The procedure was carried out using either SUMMIT® SI OCT Spinal Fixation System Instruments (DePuy Synthes, USA; $n = 54$) or Synapse™ OCT system (DePuy Synthes, USA; $n = 6$). Skin incision was linear and muscular stage was performed in a standard manner.[14] Occipital plating was done if gross atlanto-occipital instability was present and for Type A basilar invagination of Goel's classification[15] with separate analysis for each group (with occipital plating versus without). Additional small maneuvers such as C1 laminectomy or reduction of the dislocation were done as necessary for relevant pathologies.

Quality of life assessment

Subjects or their caregivers were communicated with and the questionnaire was presented to them. EQ-5D-3L Paper Telephone v2.0 (ID 71378) and EQ-5D-Y Paper Proxy1 v1.0 (ID 54602) were used (EuroQol Group, Rotterdam, The Netherlands). Preoperative quality of life was assessed as well as the quality on the day of the follow-up. EQ-5D is a tool commonly used in spine surgery evaluating HRQoL.[16,17] It assesses five domains: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression. The score is obtained in the form of a five-digit number that depicts the patient's health state. This five-digit number is then transformed into measurable and convenient utility by means of the standardized chart.[12] Results range from −1 to 1. 0 is equal to death and 1 is equal to perfect health. Negative

values are interpreted as HRQoL that is worse than death as perceived by a given individual. In addition, patients were also asked to depict their HRQoL in a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Finally, following methods described elsewhere,[10] EQ-5D values were compared with the HRQoL of the age-matched representatives from the national database in Poland[12,13] so as to determine the size of a potential gap between the CCJ subjects following surgery and the general population. Another matching was performed for comorbidities so as to visualize the difference between HRQoL of patients with CCI and of those with similar conditions without CCI. Both matchings were conducted on a many-to-many basis.

Software and measurements

By means of OsiriX MD 11.0 (Pixmeo SARL, Bernex, Switzerland), the following items were measured by two observers (a neurosurgical resident and neurosurgeon): (1) atlanto-dental interval, (2) revised condyle-C1 interval, (3) dens to McRae line, (4) dens to Chamberlain line,[5] dens to McGregor line, (6) dens to Wackenheim, (7) basion-axial interval, (8) basion-dental interval, (9) C2 isthmus height and internal height to determine if HRVA is present, (10) Powers ratio, (11) sagittal diameter of spinal canal at the level of C1 and foramen magnum, and (12) C2 pedicle width to detect narrow pedicles. Normal limits were retrieved from the studies of Kanodia *et al*., Pawar *et al*., Ulbrich *et al*., Dahdaleh *et al*., and Marathe *et al*.[18-22] Prevalence of high-riding vertebral arteries (isthmus height ≤5 mm or/and C2 internal height ≤2 mm) and narrow pedicles (C2 pedicle width <4 mm) was determined only in adults since pediatric norms have not been established.[23,24] Every measured parameter was included in the correlation analysis. For significant measurements in correlation analysis, inter-software and inter-observer agreement coefficients were analyzed to determine reproducibility. Inter-software reliability between the primary software (OsiriX MD) and RadiAnt DICOM Viewer version 2020.2 (Medixant, Poznan, Poland) was acknowledged by kappa statistic ranging from −1 to 1, with 0 equal to randomness, and 1 indicating perfect reproducibility. As widely accepted, the kappa values were interpreted as: <0.20 poor reliability, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and >0.80 excellent reliability. To increase reliability, the observers obtained a standardized instruction in PowerPoint slideshow (Microsoft, Redmond, USA) delineating measurements, finalized with measuring ten nonrelated cases, question-and-answer session, and debriefing.

Statistical analysis

Statistical analysis was performed by means of RStudio version 1.3.1093 (Boston, Massachusetts, USA) and Statistica 13.3.0, TIBCO Software Inc. (Palo Alto, California, USA) by TK. Medians were supplemented with corresponding interquartile ranges (IQRs) whereas means with standard deviations (SD). For testing a null hypothesis of equal medians with regard to pre- and postoperative nonparametric outcomes, a Wilcoxon test was used. Spearman's rank correlation rho was estimated for each classic radiologic measurement and the follow-up HRQoL. Multiple linear regression analysis was conducted to determine factors correlating with an outcome of interest at follow-up. A linear adaptation of the HRQoL trajectory based on multiple regression was created in RStudio with ggPredict().

RESULTS

Cohort characteristics

The subject characteristics are presented in Table 1. Of sixty subjects who underwent posterior craniocervical instrumentation between 2006 and 2021, thirty were

Table 1: Study group characteristics

Feature	Value
Sex (%)	
Female	30 (50.0)
Male	30 (50.0)
Age (years)	37.2±26.5
CCI cause (%)	
Traumatic	24 (40.0)
Congenital	16 (26.7)
Rheumatic	12 (20.0)
Tumor	6 (10.0)
Grisel syndrome	1 (1.7)
Levels of instrumentation (%)	
O-C1-C2	18 (30.0)
O-C1-C2-C3	10 (16.7)
C1-C2	16 (26.7)
C1-C2-C3	9 (15.0)
Others	7 (11.7)
Duration of surgery (min)	224 (IQR 170-268.8)
Blood loss (mL)	320 (IQR 200-500)
Age >18	415 (IQR 300-537.5)
Age <18	200 (IQR 100-325)
Hospital stay (days)	10 (IQR 9-17)
HRQoL (EQ-5D-3L summary index)	
Total preoperative	0.254 (IQR=-0.025-0.504)
Total at follow-up	0.779 (IQR=0.387-0.864)
Age >18 preoperative	0.224 (IQR 0.090-0.390)
Age >18 follow-up	0.739 (IQR 0.275-0.868)
Age <18 preoperative	0.284 (IQR-0.176-0.716)
Age <18 at follow-up	0.814 (IQR 0.462-0.853)
Neurological status (%)	
Myelopathy preoperative	41 (68.3)
Improved postoperative	22 (53.7)
Stable postoperative	16 (39.0)
Deteriorated postoperative	3 (7.3)

CCI: Craniocervical instability, HRQoL: Health-related quality of life, IQR: Interquartile range

females (50%) and thirty were males (50%). The mean age of the group at the time of operation was 37.2 years (SD = 26.5). The median time from the procedure until the last follow-up was 26.3 months (IQR = 10.8–47.3). The most common cause of CCI was trauma (n = 24; 40%). Of traumatic patients, falls (n = 11; 45.9%) and motor vehicle accidents (n = 7; 29.2%) prevailed. The most common type of CCI was atlantoaxial instability (n = 38; 63.3%), followed by combined atlantoaxial and atlantooccipital instabilities (n = 12; 20.0%). Pure atlantooccipital dislocation was observed in eight subjects (13.3%). In two cases, it was undetermined. Neurological deficits due to spinal cord compression (myelopathy) were present preoperatively in 71.4%. The most common levels of instrumentation were as follows: O-C1-C2 in 18 cases (30.0%) and C1-C2 in 16 cases (26.7%). The occiput was plated in 35 subjects (58.3%). The median duration of the surgery was 224 min (IQR = 170–268.8). The median blood loss in the entire cohort was 320 ml (IQR = 200-500). Unsurprisingly, the median blood loss was higher in adults than in those under 18 years old (415 ml and 200 ml, respectively). The median hospital stay was 10 days (IQR = 9–17).

Quality of life evaluation

The median timing of the second questionnaire was 26.3 months after surgery (IQR = 10.8–47.3). The median preoperative EQ-5D was 0.254 (IQR = −0.025 to 0.504), whereas the median follow-up EQ-5D was 0.779 (IQR = 0.387–0.864). The difference was statistically significant ($P < 0.001$). The median improvement in the HRQoL was estimated at 0.508 (IQR = 0.128–0.717), which exceeds the minimum clinically important difference.[25] Despite the increase, the EQ-5D at follow-up score was still below the 25th percentile (0.894) of the general Polish population age-matched on a many-to-many basis.[13] The median preoperative HRQoL in the Visual Analog Scale (VAS) from 0 (worst imaginable health state) to 100 (best imaginable health state) was declared to be 40 (IQR = 20–50), while postoperatively, it was 70 (IQR = 52.5–80) with a median increase of 30 (IQR = 10–45). The improvement was statistically significant ($P < 0.001$). The median VAS EQ-5D of the age-matched general population is 80, whereas the 25th percentile is 73. A tabular display of comparison with the comorbidity-matched and age-matched datasets is presented in Table 2. Comorbidity-matched values are retrieved from the studies of Schwab *et al*., Koga *et al*., Hurst *et al*., and Bond *et al*.[10,26-28]

Preoperatively, domains of health that were negatively affected most often were pain/discomfort and anxiety/depression – 94.4% of subjects reported at least moderate problems with each [Figure 1]. At follow-up, on the other hand, pain/discomfort and usual activities were disturbed the most. Preoperatively, HRQoL dimension that was the least influenced was self-care as 19.4% declared no problems at all, half of the responders had moderate difficulties, and 30.6% were unable to wash or dress themselves. At follow-up, however, walking was the area that most subjects had no problems coping with.

Table 2: EuroQol-5 dimensions summary indices and Visual Analog Scale in craniocervical instability prior to craniocervical fixation, postoperatively, in comorbidity-matched and age-matched datasets

	EQ-5D summary index	EQ-5D VAS
Subjects with CCI preoperatively (this study)		
Entire cohort	0.254	40
Rheumatoid subgroup	0.103	20
Traumatic subgroup	0.125	35
Congenital disorder subgroup	0.187	40
Craniocervical tumor subgroup	0.535	45
Comorbidity-matched population without CCI		
Rheumatoid arthritis functional level 3	0.120	44
Spinal C1-C4 trauma	0.317	50
Congenital disorders	N/A	70
Cervical spine tumor	0.780	65
Subjects with CCI postoperatively (this study)		
Entire cohort	0.779	70
Rheumatoid subgroup	0.743	50
Traumatic subgroup	0.730	65
Congenital disorder subgroup	0.794	70
Craniocervical tumor subgroup	0.894	80
Age-matched general population	0.894*	73*

*Values representing the 25th percentile of the age-matched population. Values are presented as medians unless stated otherwise. Age-matched values are retrieved from the study of Golicki and Niewada.[13] EQ-5D: EuroQol-5 dimensions, CCI: Craniocervical instability, CCJ: Craniocervical junction, VAS: Visual Analog Scale, N/A: Not available

The medians of preoperative HRQoL in the groups with or without occiput plating were as follows: 0.100 and 0.310, respectively (nonsignificant difference; P = 0.069). The medians of the follow-up HRQoL in the same groups were 0.670 and 0.810, respectively (P = 0.061). The median increments of HRQoL in these groups were 0.540 and 0.400, respectively (P = 0.692) indicating similar results in terms of HRQoL gain in both groups. In multiple linear regression model, the outcome of interest (HRQoL at follow-up) was significantly affected by age (β = −0.004; P = 0.049) and length of the hospital stay (β = −0.134; P = 0.010). It was not influenced either by plating the occiput (P = 0.495) or neurological status upon discharge (P = 0.234) [Table 3]. A trajectory of HRQoL based on this regression model involving the significant predictors is presented in Figure 2.

Radiologic measurements

The summary of radiologic evaluation is presented in Table 4. 19.05% had at least one high-riding vertebral artery and

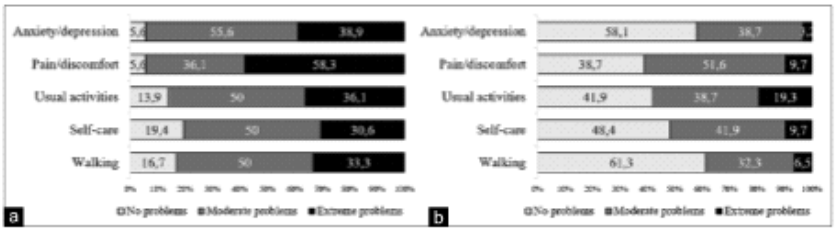

Figure 1: Distribution of the (a) preoperative and (b) follow-up domains regarding health-related quality of life in EuroQol-5 dimensions questionnaires

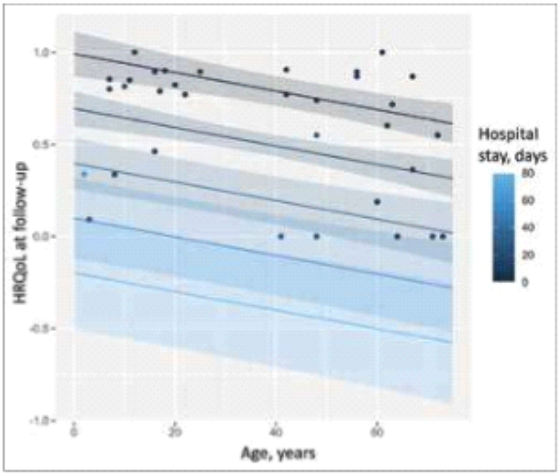

Figure 2: A graph illustrating multiple regression model with two statistically significant predictor variables (age and length of hospital stay). Health-related quality of life regarded as EuroQol-5 dimensions-3L summary index

33.33% presented with at least 1 narrow pedicle. Parameters that were abnormal most commonly on the preoperative assessment were dens to the McRae line (71.43%) and to the Wackenheim line (60%). On postoperative scans, these two prevailed as well. Of all the classic radiologic markers, only preoperative dens to Wackenheim line correlated with HRQoL at follow-up (rho = −0.432; P = 0.028; moderate correlation). Despite the significant correlation, linear regression did not prove the preoperative Wackenheim line to be a predictor (β = −0.291; P = 0.0806). For Wackenheim parameter, Cohen's kappa of inter-software reliability was κ_1 = 0.8148, Z = 4.91 (excellent), whereas kappa of inter-observer agreement was κ_2 = 0.75, Z = 4.58 (good).

DISCUSSION

Quality of life in spinal disorders

EQ-5D scores have been established for a variety of spinal conditions. For instance, Smith *et al.*[29] in 2017 presented HRQoL in adult cervical deformity (ACD), of which EQ-5D-3L summary index was 0.511 (SD = 0.224). It was below the lower 25th percentile for the age-and gender-adjusted general population. Similar to our findings, the dimension of the worst quality was pain/discomfort. Better HRQoL in ACD than in CCI might be explained by the typically chronic nature of the first one. Since ACD progresses more slowly, patients are able to adapt to it, which is to the contrary of acute disorders. Therefore, subjects with acute vertebral fragility fractures demonstrate low EQ-5D-3L scores: 0.27 (95% confidence interval [CI] 0.22–0.31),[27] which is very close to the findings of the present study: 0.254 (IQR = −0.025 to 0.504). Another similarity between vertebral fractures and CCI is a substantial improvement after successful treatment. The former increases up to 0.69 (95% CI 0.66–0.72) and the latter up to 0.779 (IQR = 0.387–0.864) at follow-up.[30] It could be elucidated by the quick resolution of debilitating dysfunctions once the segments are stabilized, the pain subsides, rehabilitation begins, and fear diminishes. Moreover, as presented in Table 2, conditions that might lead to CCI (rheumatoid arthritis, cervical trauma, congenital disorders, and cervical spinal tumors) decrease HRQoL *per se*. Therefore, bimodal matching was executed: for comorbidities to analyze the real burden of CCI and separately for age to detect the gap between subjects after successful treatment and general population. Occurrence of CCI further exacerbates the damage and reduces life quality. As demonstrated in this study, posterior fixation of the craniocervical junction involving C1-C2 aids in this aspect, especially in terms of pain/discomfort and anxiety/depression.

Table 3: Summary of the multiple regression model to predict an outcome variable (health-related quality of life regarded as EQ-5D at follow-up) on the basis of four predictor variables

Variable	EQ-5D score at follow-up	
	β	*P*
Age (years)	−0.004	**0.049**
Occiput plating	0.073	0.495
Hospital stay (days)	−0.134	**0.010**
Neurological status at discharge	0.072	0.234

Statistically significant predictors are bolded

Predictors of the health-related quality of life

Multiple linear regression model of four factors (chosen based on a recent meta-analysis[31]) yielded significant predictors for HRQoL at follow-up, which are age and length of the hospital stay. Older subjects and those who are hospitalized

Table 4: Summary of the pre- and postoperative radiologic evaluation

Parameter	Normal limits (mm)	Number of subjects with abnormal preoperative (%)	Number of subjects with abnormal postoperative (%)	Spearman's rho for postoperative HRQoL*	*P* value for rho*
ADI	<3 (a) <5 (p)	7/34 (20.59)	5/32 (15.63)	0.061-0.017	0.767 0.937
rCCI					
Left	<2.5	7/35 (20)	8/35 (22.86)	-	-
Right		5/35 (14.29)	8/35 (22.86)		
Dens to McRae line	≥5 below	25/35 (71.43)	26/33 (78.79)	-0.192-0.147	0.348 0.503
Dens to Chamberlain line	<3 above	13/35 (37.14)	7/27 (25.93)	-0.139-0.347	0.509 0.146
Dens to McGregor line	<4.5 above	13/35 (37.14)	7/27 (25.93)	-0.183-0.131	0.382 0.593
Dens to Wackenheim line	Ventral or tangential	21/35 (60)	19/33 (57.58)	**-0.432** 0.093	**0.028** 0.672
BDI	<8.5	7/35 (20)	7/33 (21.21)	-0.090 0.094	0.660 0.668
BAI	−4-+12	19/35 (54.29)	13/33 (39.39)	-0.140 0.004	0.492 0.986
Sagittal diameter at C1	>22	11/31 (35.48)	4/24 (16.67)	0.295 0.049	0.172 0.858
Sagittal diameter at FM	>30	6/35 (17.14)	4/35 (11.43)	-0.021 -0.069	0.917 0.747
Powers ratio		5/30 (16.67)	2/23 (8.70)	-0.416 -0.418	0.054 0.121
Cortical breach	No breach	-	14/35 (40)	-0.090	0.677

*Upper number describes rho or *P* value of the preoperative radiologic parameter, lower number describes rho or *P* value of the postoperative radiologic parameter. Statistically significant rho/*P* values are bolded. a: Adults, p: Pediatrics, ADI: Atlantodental interval, rCCI: Revised condyle-C1 interval, BDI: Basion-dens interval, BAI: Basion-axial interval, FM: Foramen magnum, HRQoL: Health-related quality of life

for long periods might have worse health-related quality of life at follow-up. Older age is associated with lower recovery capabilities, hindered rehabilitation, and a plethora of comorbidities, all of which add up resulting in prolonged difficulties with walking, self-care, and usual activities. Although pain can often be controlled pharmacologically, disturbed activities of basic living provoke anxiety, and fear.[31] Thus, people after CCJ fusion might require further psychological help. The other factor that could predict HRQoL is duration of the hospital stay. It is often a reflection of the complications such as acute postoperative respiratory failure requiring intensive care, wound infection, or dehiscence. Interestingly, occipital plating did not prove significant here for the follow-up life quality as it did for neurological outcome in the recent meta-analysis of posttraumatic cohort conducted by Klepinowski *et al*.[3] This might be stemming from a number of different causes such as more heterogeneous cohort in the present study, lower number of subjects, or lack of direct translation from neurological status into HRQoL.

The significant Spearman's correlation rho between the Wackenheim line parameter and HRQoL should be interpreted cautiously. As Kwong *et al*.[32] demonstrated, the Wackenheim clivus line is dependent upon the neck position and, thus, at times might be unreliable. Since linear regression denied it as a predictor, the causality remains uncertain. For it was close to the threshold of significance, studies of larger samples could potentially detect it as an important early preoperative predictor of the follow-up quality of life. Moreover, as presented in Table 3, the Wackenheim parameter changed very little after the procedure. This is a sequela to the fact that the invaginated dens are often difficult to reduce, especially in rheumatoid arthritis or congenital abnormalities. In light of this information, in such situations, one should carefully consider the risk and benefits of extending surgery to transoral approach so as to decompress the brainstem.

Implications

This is the first study to touch upon the HRQoL after craniocervical instrumentation in both adults and pediatrics. HRQoL could possibly be the most important piece of outcome from the patient's perspective. There is no radiologic, laboratory, or a single clinical measure that would provide as much valuable data as life quality, yet it is often neglected in the final assessment. Knowledge of the preoperative baseline and the follow-up records could serve as background for future comparisons and discussions. Quantification of the HRQoL allows health-care providers to perform cost–utility analysis of the procedure. Appreciation of the domains of HRQoL that deviate the most after fusion

could indicate which aspects need more focus and resource allocation. Determination of the potential clinical and radiologic predictors might aid patient and family counseling, especially for the elderly and of the long hospital stay. Finally, the limitations acknowledged in this study might guide the upcoming studies to furnish stronger evidence and clinical guidelines regarding craniocervical fusion.

Limitations

Despite being contributory to the body of neurosurgical literature, this study has several flaws. First of all, this research constitutes only level 3 evidence. Although it is the best we currently have, undoubtedly studies of prospective case–control design would be appreciated to provide stronger data. Second, a number of patients could not be reached for the follow-up EQ-5D questionnaire due to an unresponsive or invalid phone number (dropout rate: 36.6%) – this was, however, taken into consideration at the stage of sample size estimation. Still, some of those unresponsive patients might have been dead or otherwise incapacitated, introducing a selection bias. This issue can only be addressed via prospective studies where it is taken into account so in such cases relatives can be reached.

Since CCI is a rare entity, the study group was heterogeneous in causes of CCJ instability. The comorbid conditions likely impact HRQoL. The authors are aware of this fact and, thus, performed matching for the comorbidities and, separately, for age. Matching for age with general population as was done here has potential to determine the gap between treated CCI and the age-matched general population. Matching for comorbidities allowed for appreciation how CCI affects HRQoL as compared with similar conditions without CCI. Overall, this is common to analyze the causes altogether due to the rarity of this condition.[7,33] Thus, large samples of each cause are possibly obtainable only through multi-institutional collaborations.

Another drawback might be that adults and pediatrics were analyzed in the same study. Even though we first considered it a limitation, it may also be considered a strong point of this work since it allowed for detection of age as an independent predictor of HRQoL at follow-up in multiple linear regression model. Moreover, in order to further mitigate the potential bias, separate subgroup analysis and HRQoL calculation were conducted for adults and children.

Posterior fixation of C1-C2 segment was performed in each subject. Some of them, however, had additional cranial or caudal extension of the stabilization. The limitation of heterogeneity of either involving the occiput or not was addressed in the subgroup analysis as well as in the multiple linear regression model to determine whether it affected HRQoL.

As Atul Goel elegantly noticed,[34] cervical range of motion is determined mostly at the craniocervical junction (O-C2), thus inclusion of the lower cervical spine in stabilization was not addressed separately.

CONCLUSIONS

HRQoL is substantially reduced in subjects with CCI, also when compared with the comorbidity-matched dataset. Yet, it can be improved with successful posterior fixation. Despite the improvement, the HRQoL is still worse than the bottom 25th percentile of the age-matched general population. Occipital plating might not affect the trajectory of HRQoL. Patients' age and length of the hospital stay could predict HRQoL at follow-up. Elderly subjects might not benefit as much as the young from the posterior fixation in terms of quality of life. The longer hospitalization, the worse HRQoL is expected. Most of the classic radiologic markers do not correlate with one's follow-up HRQoL. Only the baseline Wackenheim line might carry such correlation, but this requires further confirmation. Results of this study could enhance patient counseling and in future might be of interest for public health when comparing posterior screw fixation with other treatment options.

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Conflicts of interest

There are no conflicts of interest.

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13.6 Oświadczenia współautorów

Szczecin, 01.04.2022r.

Oświadczenie o procentowym udziale autorów publikacji naukowej

Management of post-traumatic craniovertebral junction dislocation: A PRISMA-compliant systematic review and meta-analysis of case reports
(tytuł publikacji naukowej)

Klepinowski, T, Limanówka, B & Sagan, L (2021) Management of post-traumatic craniovertebral junction dislocation: A PRISMA-compliant systematic review and meta-analysis of case reports. Neurosurg Rev. 44:1391–1400; https://doi.org/10.1007/s10143-020-01366-4
(dane bibliometryczne z doi)

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Prevalence of high-riding vertebral arteries and narrow C2 pedicles among Central-European population: a computed tomography-based study

(tytuł publikacji naukowej)

Klepinowski T, Żyłka N, Pala B, Poncyljusz W, Sagan L (2021) Prevalence of high-riding vertebral arteries and narrow C2 pedicles among Central-European population: a computed tomography-based study. Neurosurg Rev. https://doi.org/10.007/s10143-021-00232

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Oświadczenie o procentowym udziale autorów publikacji naukowej

Risk of the high-riding variant of vertebral arteries at C2 is increased over twofold in rheumatoid arthritis: a meta-analysis

(tytuł publikacji naukowej)

Klepinowski T, Cembik J, Sagan L (2020) Risk of the high-riding variant of vertebral arteries at C2 is increased over twofold in rheumatoid arthritis: a meta-analysis. Neurosurg Rev. 44: 2041–2046; https://doi.org/10.1007/s10143-020-01425-w

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Prevalence of High-Riding Vertebral Artery: A Meta-Analysis of the Anatomical Variant Affecting Choice of Craniocervical Fusion Method and Its Outcome
(tytuł publikacji naukowej)

Klepinowski T, Pala B, Cembik J, Sagan L (2020) Prevalence of high-riding vertebral artery: a meta-analysis of the anatomical variant affecting choice of craniocervical fusion method and its outcome. World Neurosurg. 143:e474–e481; https://doi.org/10.1016/j.wneu.2020.07.182
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EQ-5D health-related quality of life questionnaire in craniovertebral instability treated with posterior fixation with or without occipital plating: a comparative study with matched datasets

(tytuł publikacji naukowej)

Klepinowski T, Sagan L (2022) EQ-5D health-related quality of life questionnaire in craniovertebral instability treated with posterior fixation with or without occipital plating: a comparative study with matched datasets. J Craniovert Jun Spine 2022;13(1):72-9. https://doi.org/10.4103/jcvjs.jcvjs_125_21

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13.7 Zaświadczenie Komisji Bioetycznej

Pomorski Uniwersytet Medyczny w Szczecinie

KB-0012/24/04/2020/Z

Szczecin, dnia 01.04.2020 r.

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W związku ze zgłoszeniem opisu badania do Komisji Bioetycznej Pomorskiego Uniwersytetu Medycznego w Szczecinie pt.: „Ocena wyników leczenia dyslokacji w obrębie złącza kręgowo-podstawnego przy użyciu stabilizacji przeznasadowej", uprzejmie informuję, iż z przedłożonej dokumentacji wynika, że przedmiotowe badanie nie wymaga opinii Komisji Bioetycznej.

Z poważaniem

PRZEWODNICZĄCY
Komisji Bioetycznej
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