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Diagnostic accuracy of serum alpha-fetoprotein levels in diagnosing recurrent sacrococcygeal teratoma: A systematic review

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ABSTRACT

Background: The incidence of children developing recurrent sacrococcygeal teratoma (SCT) is 2–35%. Serum alpha-fetoprotein (AFP) is often used as a tumor marker for (malignant) recurrences of SCT and could potentially be used during routine follow-up after SCT resection. However, the diagnostic accuracy of serum AFP levels during follow-up has not been well established. Therefore, we aimed to systematically review the diagnostic accuracy of serum AFP levels in recurrent SCT.

Methods: We queried Search Premier, COCHRANE Library, EMCARE, EMBASE, PubMed, ScienceDirect and Web of Science databases to identify studies regarding patients with SCT with follow-up using serum AFP levels postoperative. We estimated sensitivity and specificity of serum AFP levels.

Results: Fifteen studies (613 patients, 121 recurrences) were included and these mainly described serum AFP levels in patients with recurrent SCT ($n = 111$); 83 (75%) patients with recurrent SCT had elevated serum AFP levels. A subgroup analysis of articles that measured serum AFP levels in all patients ($n = 6$, 136 patients, 14 recurrences) showed a sensitivity and specificity of 79% and 95%, respectively. The sensitivity of AFP levels to detect malignant recurrence was 96%.

Conclusion: Diagnostic accuracy of serum AFP levels to detect recurrent SCT seems promising, though sensitivity could be overestimated since serum AFP levels are mainly described in patients with elevated AFP levels or at recurrent SCT. Furthermore, serum AFP levels could be helpful to detect malignant recurrences.

Type of study: Systematic review of level 2–4 studies.

Level of evidence: Level 2–4 (mostly level 2).

Contents

Abbreviations: AFP, Alpha-fetoprotein; FU, Follow-up; PRISMA, Preferred Reported Items for Systematic Reviews and Meta-Analysis statement; PROSPERO, International Prospective Register of Systematic Review; SCT, Sacrococcygeal teratoma; YST, Yolk sac tumor.

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Sacrococcygeal teratoma (SCT) is the most common neonatal tumor with a reported incidence of 15,000 to 35,000 with a male:female ratio of 1:4 [1,2].

SCTs can be diagnosed prenatally with fetal ultrasound and approximately 80% of patients are diagnosed within the first month after birth [3]. Malignant disease at the time of initial diagnosis occurs in 11–35% of patients [4]. The likelihood of malignant transformation in SCT increases with age, resulting in malignancy rates up to 70% if SCT is diagnosed at the age of one year [5].

Surgical resection is the preferred treatment of SCT. Children with malignant teratomas are treated with chemotherapy in addition to surgical resection. This approach leads to an overall survival rate of 90% for malignant teratomas after 12 years [6]. The recurrence risk of SCTs after resection is 12.5% (range 2–35%) [5,7,8]. Mature SCT has a mean recurrence rate of 10%, and immature and malignant SCTs have mean recurrence rates of 33% and 18%, respectively [9]. Recurrence pathology shows a shift towards malignancy; 22–56% of recurrences have some evidence of malignant yolk sac tumor (YST) [1,9–11]. Established risk factors for local recurrence are incomplete resection of the tumor or coccyx, tumor spillage during primary resection and microfoci of YST on pathological evaluation [5].

Oncological follow-up of patients treated for SCT is recommended for at least three years and includes physical examination, radiological imaging and serum alpha-fetoprotein (AFP) levels [4].

AFP is often used as a tumor marker for malignant germ cell tumors and malignant recurrences of SCT [6]. Levels of serum AFP are usually increased in the neonatal period, since this protein is normally synthesized in the fetal liver and yolk sac. Values should normalize within months after birth. AFP serum levels that exceed normal, age related concentration or increasing serum AFP levels can be used as a first sign of malignant relapse after surgical resection of SCT [12,13]. However, the diagnostic accuracy of serum AFP levels in order to detect recurrent SCT after resection has not been well established.

The aim of this systematic review is to assess the diagnostic accuracy of serum alpha-fetoprotein levels in detecting a recurrent SCT.

1. Methods

1.1. Protocol

A systematic review was conducted in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement on literature regarding the diagnostic accuracy of serum AFP levels in recurrent sacrococcygeal teratoma. The protocol was registered (PROSPERO 2019: CRD42019117193).

1.2. Literature search

We queried Academic Search Premier, COCHRANE Library, EMCARE, EMBASE, PubMed, ScienceDirect and Web of Science databases and reference lists of eligible articles for the selection of studies. The search strategy was conducted in August 2019 (Appendix A).

1.3. Eligibility criteria

Studies were considered eligible when written in English and published after December 1980. Inclusion criteria were (a) children with sacrococcygeal teratoma, (b) follow-up after resection with serum AFP levels and (c) serum AFP levels were provided in numbers. Studies which were (a) written in another language than English, (b) case reports, and (c) publications before 1980 were excluded from data analysis.

1.4. Study selection and methodological quality assessment

Two reviewers (MK and LH) independently performed the screening and selection of articles based on title and abstract, and final on full text. The Newcastle Ottawa Quality Assessment Scale for Cohort studies checklist [14] was used independently to assess the methodological quality of the included studies. A third independent reviewer (JD) author solved inconsistencies by a second review of the literature.

1.5. Data extraction and analysis

Appendix B comprises data that were systematically extracted from the studies included in this systematic review by the two reviewers and recorded in data collection. Missing data were calculated when possible and unpublished data or further details were retrieved by contacting study author(s).

2. Results

2.1. Literature search

Literature search yielded 726 potentially eligible studies. Duplicates were removed and 648 records were excluded after the initial screening. Thirty more records were excluded after full text screening. Fifteen studies were included in this review (Fig. 1).

2.2. Study characteristics

The 15 selected studies were published between 1991 and 2019 and included 613 children with SCT. There were 142 males and 370 females with a male:female ratio of 1:2.6. In 101 patients, sex was not described. Age at primary surgery ranged from prenatal (gestational age of 21 weeks) to 17.5 years. Study characteristics are described in Table 1. The histological diagnosis was mature teratoma in 334 (56.4%), immature teratoma in 57 (9.6%) and malignant in 201 (34.0%) patients. In 21 patients, histology was not described.

Follow-up duration ranged from three to 156 months and consisted of biomarkers (three studies), physical examination and biomarkers (one study), imaging modalities and biomarkers (one study), physical examination, imaging modalities and biomarkers (seven studies), or was not described (three studies).

2.3. Methodological quality

The Newcastle Ottawa quality assessment scale [14] was used to determine the quality of the included studies. In 12 studies, quality was considered good and in three [6,15,16] poor (Appendix C).

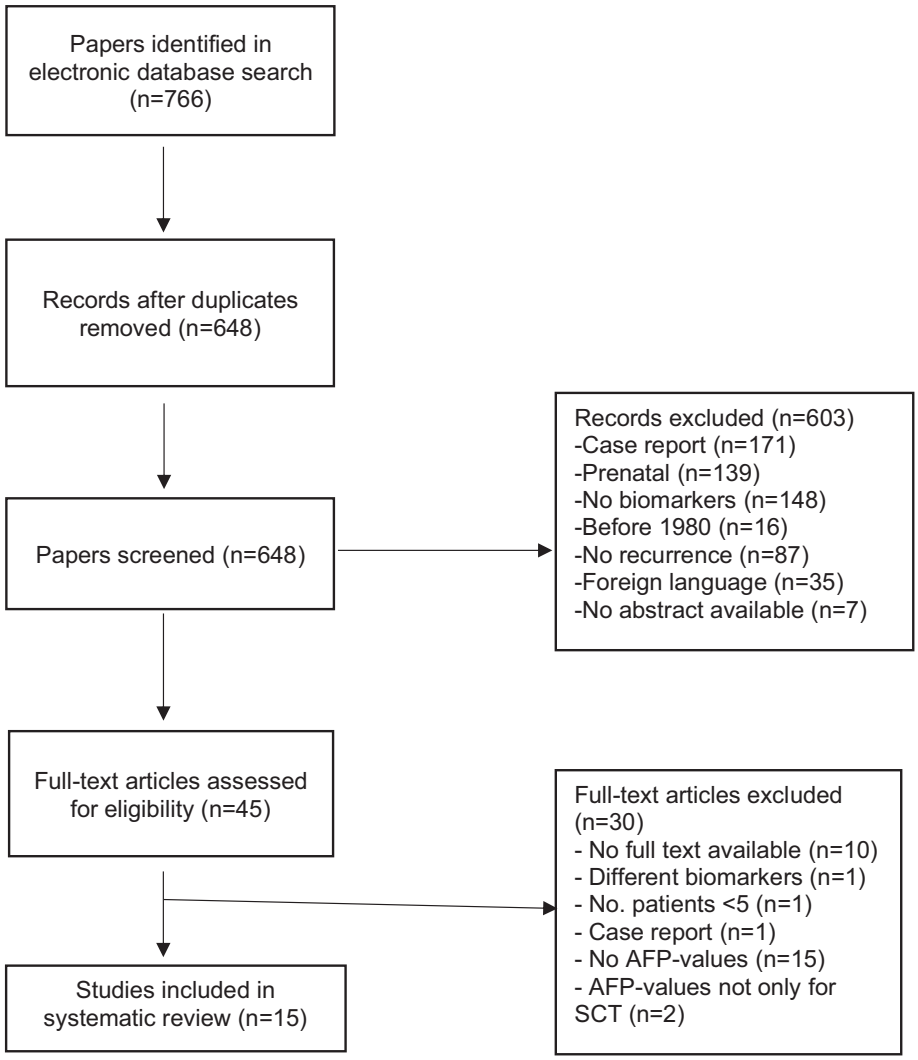

Fig. 1. PRISMA flowchart of the study selection

2.4. Patients with recurrent SCT

One hundred eleven patients developed 121 recurrences. The mean percentage of patients with recurrent SCT was 18.1% (range 0–33.3%).

In 93% of the patients, age ranged from two to 42 months. There were eight outliers: one developed recurrence at 59 months, three at 84 months, two at 96 months and two at 204 months of age [1,9–11,17]. This histological diagnosis of the recurrent tumor was mature teratoma in one, immature teratoma in one and malignant in five patients. In one patient, histology was not described.

Median latency period to recurrence was described in six studies; these ranged from 1.3 to 42 months [1,9,11,15,18,19]. The histological diagnosis of the recurrent tumor was mature teratoma in 24 (19.8%), immature teratoma in 10 (8.3%) and malignant in 85 (70.2%) patients. In two (1.7%) patients, histology was not described.

2.5. AFP levels in recurrent SCT

AFP levels were evaluated in all studies. However, it was not evaluated in all patients. Serum AFP levels were described for 233 patients (Table 2). In this group, 111 (47.6%) patients developed recurrence. In 83 patients, serum AFP levels were elevated at time of recurrence. In 25 of these patients, elevated AFP levels were measured before recurrence could be clinically detected. Histology showed that 18 of them had malignant recurrence, five immature and two mature recurrence. Furthermore, 28 children developed recurrence without elevated serum AFP levels. Nineteen had a mature recurrence, six immature and three malignant recurrence. Seven children had elevated AFP levels without recurrence. Elevated serum AFP levels in recurrent SCT ranged from 76 to 217,200 μg/l.

Since most studies provided AFP levels only for patients with recurrence, subgroup analyses were performed.

The nonrecurrent subgroup consisted of six studies that also provided AFP levels for the majority of nonrecurrent patients [10,15,16,18,20,21]. AFP levels were reported for 136 (87.7%) of the 155 patients included in these studies. Recurrence was reported in 22 (16.2%) patients of whom six had mature teratoma, three immature, ten malignant and in three patients, pathology was not mentioned. Of the patients with recurrence, 11 patients had elevated AFP levels of whom one with immature and ten with malignant teratoma. Three patients developed recurrence with normal AFP levels: two mature and one immature teratoma. In the other eight patients AFP levels were measured but not described: four with mature, one with immature, one with malignant teratoma and in two patients, pathology was unknown. Six patients had elevated AFP levels without developing recurrent disease.

In the malignant recurrent subgroup, all malignant recurrences ($n = 85$) of all studies were included. In 83 patients AFP levels were measured and 80 had elevated values.

Table 1
Study characteristics of the included studies ($n = 15$).

Author	Year	Country	Study design	SCT patients (n)	Male (%)	Female (%)	Age at primary surgery	Follow-up duration (months)	Recurrences (*n*) (%)	Elevated AFP levels at recurrence (*n*)	Elevated AFP levels (ng/ml)	Normal AFP levels at recurrence (*n*)	Cutoff AFP levels
Barreto [21]	2009	Brazil	Retrospective cohort study	6	1 (16.7)	5 (83.3)	First or second day of life	34–44 (mean 39)	0 (0)	0	-	-	8–18 ng/ml
Bilik [19]	1993	Canada	Retrospective cohort study	28	3 (10.7)	25 (89.3)	First 7 days of life	30.1–62.3	6 (21.4)	3	7326.7 ± 4630.3	3	-
Büyükpamukcu [17]	2012	Turkey	Retrospective cohort study	58	20 (34.5)	38 (65.5)	-	156	19 (32.8)	13	61–12,154	4	10 ng/ml
De Corti [6]	2012	France, Italy	Retrospective cohort study	57	11 (19.3)	46 (80.7)	Mean 2 days old (range 0–115 days)	72 (3–148.8)	19 (33.3)	19	4244 (241–177,800)	0	According to TGM 95 protocol of the SFCE[32]
Havrànek [15]	1992	Sweden	Retrospective cohort study	32	11 (34.4)	21 (65.6)	-	12–108	6 (18.8)	6	150–400	0	25 ng/ml
Heerema-McKenney [22]	2005	USA	Retrospective cohort study	18	Unclear	Unclear	Antenatal: 29.83 (21–40) weeks; Postnatal: 46.6 (36–40) weeks]	37.6	0 (0)	-	-	-	10 ng/ml
Niramis [18]	2015	Thailand	Retrospective cohort study	57	13 (22.8)	44 (77.2)	1 day-5.6 years (mean 43 days, 281.9 +/− 439.6 days).	8–120	3 (7.3)	1	2000	2	20 ng/ml
Kouranloo [2]	2006	Iran	Retrospective cohort study	26	6 (23.1)	20 (76.9)	First two weeks of life	3–156	8 (30.8)	8	7320 ± 4510	-	
Lahdenne [20]	1991	Finland	Case–control study	10	Unclear	Unclear	In first week after birth	24	1 (10)	1	1419	-	Determined from 141 serial serum samples from 15 preterm infants and 62 samples from 12 healthy term infants.
On Ho [16]	2010	Australia	Retrospective cohort study	17	7 (41.1)	10 (58.9)	0–52 days (mean 10.1 days)	32	3 (17.6)	-	-	-	<10 IU/ml
Padilla [1]	2017	USA	Retrospective cohort study	40	Unclear	Unclear	0–2.5 years (mean 2 days)	-	7(17.5)	2	1735–14,960	5	Reference values according to Blohm et al. [27]
Pauniaho [10]	2010	Finland	Retrospective cohort study	33	Unclear	Unclear	-	84–96	9 (27.3)	3	2.6–56.5 MoM*	1	References values according to Lahdenne et al. [20] Values >2.5 MoM [2] were regarded elevated
Sayed [23]	2012	Egypt	Retrospective cohort study	19	7 (36.8)	12 (63.2)	-	48	5 (26.3)	3	3300–217,200	2	References values according to Blohm et al. [26]
Wang [9]	2017	China	Retrospective cohort study	105	27 (25.7)	78 (74.3)	1 day–12 years (mean 10.2 months)	51.2	19 (18.1)	15	76.18–58,326.7	4	-
Yao [11]	2014	China	Retrospective cohort study	107	36 (33.6)	71 (66.4)	0 days–17.5 years (mean 14 months)	48.9	16 (15)	9	109–121,000	-	-

1. Société Française des Cancers de l'Enfant (SFCE) [32].
2. 2.5 multiples of median (MoM) determined by Lahdenne et al. [20].

Table 2
Serum AFP values from all articles.

Serum AFP-values	SCT		Total
	Recurrence	No recurrence	
Elevated	83	7	90
Normal	28	115	143
Total	111	122	233

2.6. Diagnostic accuracy

Eighty-three of 111 patients with recurrence had elevated AFP levels. (Table 2) One-hundred fifteen of 122 patients without recurrence had normal AFP levels during follow-up. Therefore, diagnostic sensitivity was 0.75 and diagnostic specificity was 0.94. Eighty-three of 90 patients with elevated AFP levels developed recurrence. One-hundred fifteen of 143 patients without elevated AFP levels had no recurrence. Therefore, positive predictive value was 0.92 and negative predictive value was 0.80.

In the nonrecurrent subgroup, consisting of six studies [10,15,16,18,20,21], a diagnostic sensitivity of 0.79 was found. In eight patients, serum AFP levels were measured but not described. One hundred-eight of the 114 patients without recurrence had normal AFP levels resulting in a diagnostic specificity of 0.95. Eleven of the 17 patients with elevated AFP levels developed recurrence resulting in positive predictive value of 0.65. One-hundred eight of 111 patients with normal AFP levels had no recurrence. Therefore, negative predictive value was 0.97.

In the malignant recurrent subgroup, including malignant recurrences, a diagnostic sensitivity of 0.96 was found.

2.7. AFP normative values

Eleven studies described normative values for AFP levels. These levels differed between studies (Table 1). Three studies used tables with age-related values [1,6,10]. Büyükpamukcu et al. [17] and Heerema-McKenney [22] et al. defined elevated serum AFP as >10 ng/ml at one year of age.

2.8. AFP levels and histology

In six studies [1,9–11,15,23], the histology of the primary tumor was compared with recurrent tumor histology (Table 3). In 18 tumors there was a shift towards malignancy. In one patient, the initial malignant tumor had shifted to mature at recurrence. In 102 recurrences, histology was correlated to AFP levels (Table 4). Serum AFP levels were elevated in 83 cases, of which 80 (96.4%) cases were malignant. Normal AFP levels at recurrence were found in 28 cases, of which 3 (10.7%) cases were malignant.

Table 3
Histology of SCTs at original operation and recurrent operation in six studies [1,9–11,15,23].

Histology before recurrence	Number of patients	Histology after recurrence		
		Mature	Immature	Malignant
Mature	217	16	1	16
Immature	37	1	5	4
Malignant	71	1	0	37

Table 4
Correlation of histology and AFP levels in recurrent SCT in all studies.

Histology	Serum AFP-levels at time of recurrence	
	Elevated *n* (%)	Normal *n* (%)
Mature	1 (1.2)	19 (67.9)
Immature	2 (2.4)	6 (21.4)
Malignant	80 (96.4)	3 (10.7)
Total number of patients	83 (100)	28 (100)

3. Discussion

In this review we aimed to systematically assess the diagnostic accuracy of serum AFP levels in recurrent SCT. The diagnostic sensitivity of serum APF levels in detecting recurrent SCT was moderate to high, ranging from 0.75 to 0.96, depending on the subgroup of patients. Diagnostic specificity was high, ranging from 0.94 to 0.95, depending on the subgroup of patients. With a sensitivity of 0.96, serum AFP levels are mostly useful to detect malignant recurrences. In recurrent SCT, it is more important to rule out the diagnosis in order to prevent patients being sent home with recurrent SCT. This leads to a high sensitivity being most important. The diagnostic accuracy of serum APF levels in detecting recurrent SCT is moderate but high in detecting a malignant recurrent SCT. This was also found by others [10,24,25] who described elevated AFP levels in YST and immature teratomas with microscopic foci of YST. This is in line with the synthesis of this protein in the fetal liver and yolk sac [12,13].

Serum AFP levels can be difficult to interpret since AFP is always elevated in neonates. Different studies used different normative values for AFP levels. This leads to heterogeneity in the study results used in this review. Three studies [1,10,23] used tables with normal AFP levels defined by age [20,26].

Limitations of this systematic review are that serum AFP levels were mostly not the main topic of the included studies. This usually led to a brief description of AFP levels during follow-up. Only 38% of patients included in this study actually had AFP testing. To overcome this problem, subgroup analysis was performed. In the nonrecurrent subgroup, 87.7% of the patients had AFP testing. Furthermore, owing to different normative values in different studies, the terms 'elevated' and 'normal AFP levels' could differ depending on the study. Another issue in all germ cell tumors is that small elements were missed in histological sampling as the large surface of the teratoma is often irregular and that the histology of the tumor is heterogeneous. [27] The lack of appropriate immunechemistry and lack of extensive sampling could contribute to missed YST [28]. As a consequence, the exact diagnostic accuracy of serum AFP levels in relation to histology remains unclear. It has been reported that secondary rise or a delayed decline of serum AFP levels is also important when diagnosing a recurrent SCT. Delayed decline of serum AFP levels was found in patients with incomplete resection or recurrence. [25] The half-life of AFP is longer in recurrent tumor than nonrecurrent tumor [29]. A gradual drop is important, with a higher value not always being a sign of recurrence [21]. In this review, most studies described absolute serum AFP levels, not the dynamic of these levels. Therefore, it was not possible to assess the diagnostic accuracy of secondary rise or delayed decline of serum AFP levels in recurrent SCT and not possible to determine cutoff points with a receiver operating characteristic (ROC) curve.

The best interval of tumor marker controls remains unclear. Others advise frequent controls (i.e. weekly) [24] or AFP monitoring every three months for at least three years after SCT resection [30]. More research is necessary to determine the best intervals for tumor markers during the follow-up of SCT and to determine the exact diagnostic accuracy of serum AFP levels in diagnosing recurrent SCT.

We recommend monitoring serum AFP levels every three months for at least three years in order to detect (malignant) recurrences of SCT after resection since most patients develop recurrence within this time period. [31] To determine whether serum AFP levels are elevated, we advise to use tables with age-related levels. [20,26] If serum AFP levels are elevated, imaging modalities are necessary to diagnose a possible recurrent SCT.

Declaration of competing interest

The authors of this manuscript declare no relationships with any companies whose products of services may be related to the subject matter of the article.

Acknowledgments

The authors would like to thank J.W. Schoones for his contribution regarding the executing and updating of the search strategy.

Appendix A. Search Strategy

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OR AB(("sacrococcyx teratoma" OR "sacrococcygeal teratoma" OR "sacrococcygeal teratomas" OR "sacrococcygeal teratomata" OR "sacro coccygeal teratoma" OR "sacro coccygeal teratomas" OR "sacrococygeal teratoma" OR "sacrococygeal teratomas") AND ("Recurrent Disease" OR "Cancer Recurrence" OR "Tumor Recurrence" OR "recurrence" OR recurr* OR "Metastasis" OR "metastasis" OR metasta* OR micrometasta* OR "Prognosis" OR "prognosis" OR progno* OR "Disease-Free Survival" OR "Disease-Free Survival" OR "alpha fetoprotein" OR "alpha-feto-protein" OR "alpha-feto-proteins" OR "alpha fetoprotein" OR "alpha fetoproteins" OR "alpha foetoprotein" OR "alpha foetoproteins" OR "alpha foeto protein" OR "alpha foeto proteins" OR "afp" OR "afps" OR "marker" OR biomaker* OR marker*))

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Appendix B. Data collected for each included study

- Name of first author, year of publication
- Country of origin
- Study characteristics
  - o Study design
  - o Study population and patients' characteristics
  - o Method of selection
  - o Primary and secondary outcome(s)
  - o Follow-up specifications
- Initial SCT
  - o Age at detection
  - o Age at operation
  - o Histology
- Recurrences
  - o Primary and secondary
  - o Age at recurrent SCT
  - o Histology
- Serum AFP levels
  - o Cut-off values
  - o Number of patients with:
    - ▪ Elevated AFP levels with recurrent SCT
    - ▪ Normal AFP levels with recurrent SCT
    - ▪ Elevated AFP levels without recurrent SCT

Appendix C. Methodological quality assessment of the included studies using the Newcastle–Ottawa quality assessment scale[13]

	Barreto 2009	Bilik 1993	Büyükpamukcu 2012	De Corti 2012	Havránek 1992	Heerema Mc-Kenny 2005	Niramis 2015	Kouranloo 2006	Lahdenne 1991	On Ho 2010	Padilla 2017	Pauniaho 2010	Sayed 2012	Wang 2017	Yao 2014
Selection															
Representativeness	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+
Non-exposed cohort	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
Ascertainment of exposure	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Outcome not present at start study	+	+	+	+	-	+	+	+	+	-	+	-	+	+	+
Comparability															
Cohorts on the basis	+	+	+	+	-	+	++	+	++	+	+	++	+	+	+
Outcome															
Assessment	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FU: >3 years	+	+	+	-	-	+	-	-	-	-	+	+	-	+	+
Adequacy of FU	+	+	+	-	+	-	+	+	+	+	-	+	+	-	-
Total	7	8	8	6	5	7	8	7	8	4	7	8	7	7	7

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