

# Solid predominant subtype in lung adenocarcinoma is related to poor prognosis after surgical resection: A systematic review and meta-analysis



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## ABSTRACT

**Background:** Recent studies have indicated that solid predominant (SP) subtype of lung adenocarcinoma (LADC) may be associated with early recurrence and worse prognosis. Hence, a systematic review and meta-analysis were performed to evaluate the association between LADC subtype and survival.

**Methods:** The MEDLINE, SCOPUS, Web of Science and Cochrane Libraries were reviewed for eligible studies in December 2017. Studies were included if they compared outcomes of patients with and without SP subtype in resection specimens of LADC patients after surgical treatment by using multivariate Cox regression analysis. A meta-analysis for overall survival (OS) and disease-free survival (DFS) was performed. The hazard ratios (HR) or odds ratios with 95% confidence intervals (CIs) from each study were used to calculate pooled HRs. Statistical analyses were performed using Review Manager 5.3.

**Results:** In total, 14 eligible studies including 12,137 LADC patients were identified, which assessed the impact of SP subtype on OS and DFS in patients treated with pulmonary resection. SP subtype was reported in 1246 (10.2%) patients and was associated with significantly worse OS (pooled HR, 1.51; 1.29–1.75) and DFS (pooled HR, 1.26; 1.14–1.40).

**Conclusions:** SP subtype is associated with significantly worse OS and DFS in patients with LADC after pulmonary resection. These data provide evidence for the integration of the distinct histological LADC subtyping into prognostic tools and guidelines for adjuvant treatment after complete surgical resection.

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## 1. Introduction

Adenocarcinoma is the most common histologic type of lung cancer accounting for almost half of all lung cancers [1]. The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) proposed a new histologic classification of lung adenocarcinoma (ADC) in 2011, recognizing five major histologic subtypes

(lepidic, acinar, papillary, solid and micropapillary) [2].

To date, a number of cohort studies including patients after surgical resection for lung adenocarcinoma (LADC) have reported unfavorable prognosis associated with solid predominant (SP) histological subtype [3–9]. Furthermore, it has been shown that the presence of SP subtype represents an additional risk factor for N1/2 lymph node involvement and early recurrence [6,10,11]. However, this reported negative impact of SP subtype of LADC after pulmonary resection has not been validated in larger studies. Thus, it is yet unclear if specific histological subtyping of LADC should be considered as a prognostic factor for overall survival in addition to the current TNM staging system. To give light upon this issue, we therefore comprehensively reviewed available data and conducted a meta-analysis to clarify whether SP subtype represents a

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### Abbreviations and acronyms

LADC	lung adenocarcinoma
SP	solid predominant
SC	solid component
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement
OS	overall survival
DFS	disease free survival
HR	hazard ratio
CI	confidence interval
IASLC/ATS/ERS	The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society
TNM	tumor-nodal-metastasis
QUIPS	Quality in Prognostic Studies
STAS	spread through air spaces
PD-L1	programmed death-ligand 1
NSCLC	non-small cell lung cancer
JCOG	Japan Clinical Oncology Group

significant prognostic factor for LADC.

## 2. Material and methods

### 2.1. Eligibility criteria

This meta-analysis was performed in accordance with the latest PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) guidelines [12] (Supplemental Table 1). Studies meeting the following criteria were considered eligible: (1) cohort studies that were published up to December 2017 and included a comparison of disease free survival (DFS) and/or overall survival (OS) between LADC patients with or without SP by means of multivariate cox regression analysis; (2) participants with pathologically confirmed LADC after pulmonary resection; (3) studies with appropriate definition of histological examination and subtyping; (4) when the same institution was reported in different studies, the one with the largest volume was included only. Studies with the following criteria were excluded: (1) editorials, letters, reviews, abstracts, case reports; (2) articles with insufficient data for the estimation of hazard ratio (HR) and 95% confidence interval (CI); (3) patients who received neoadjuvant treatment.

Studies were included only if tumors were reviewed using comprehensive histological subtyping, recording the percentage of solid component in 5% increments according to the IASLC/ATS/ERS classifications [2]. SP is defined as the most dominant subtype of solid histologic component.

### 2.2. Search strategy

Two investigators (N. M. and K. N.) independently reviewed the PubMed (National Library of Medicine, Bethesda, MD), SCOPUS (Elsevier, Amsterdam, the Netherlands), Web of Science (Clarivate Analysis, Manchester, UK) and Cochrane Library (John Wiley & Sons, Inc. London, UK) databases for eligible articles in December 2017. A Boolean search term combination was used as follows: (component OR predominant OR pattern OR subtype OR minor) AND (resect OR resection OR operate OR operation OR lobectomy OR sublobectomy) AND (cancer OR carcinoma OR tumor) AND (lung OR pulmonary) AND solid. Potentially relevant articles were further screened by reviewing titles and abstracts. Relevant full

articles were evaluated in order to identify studies meeting the eligibility criteria.

### 2.3. Data extraction

Two independent investigators (N. M. and K. N.) extracted data including: (1) first author, publication year, study country of origin, period of study, study type, follow-up; (2) sample size, age, gender, type of surgery, study size, percentage of patients with SP subtype, stage, methods used to diagnose solid component; (3) survival data for OS and DFS with HR and 95% CI. HR estimated by multivariate analysis. If overlapping data were presented in several publications from the same data source, only the latest published article was included into the meta-analysis.

### 2.4. Assessment of study quality

The risk of bias using the Quality in Prognostic Studies (QUIPS) tool was independently assessed by two authors (N.M. and K.N.) [13]. Each domain was rated as being at low, moderate or high of bias, based on whether the study sample adequately represented the population of interest; whether the participants not being lost to follow-up adequately represented the study sample; whether prognostic factors and outcomes of interest were measured similarly for all participants; and whether there were other sources of bias. Any disagreement was discussed and a consensus was reached.

### 2.5. Statistical analysis

We extracted HRs and 95% CIs estimated by multivariate analysis from each eligible observational study conducted in LADC patients to calculate the adjusted pooled HRs. The influence of SP subtype on DFS and OS was analyzed by using the HRs and 95% CIs. Statistical heterogeneity between studies was assessed using the Cochrane Q test and by calculating the  $I^2$  value [14]. High heterogeneity was regarded as an  $I^2$  value greater than 50% or p value less than 0.05 [14]. The pooled HR and the 95% CI were estimated using the fixed-effect model in the case that heterogeneity was not detected; if not, the random-effect model was used [15].

Publication bias was evaluated by funnel plot if the included studies were more than 10 [16]. A significant p value was defined as  $p < 0.05$ . This comprehensive meta-analysis was performed using the Review Manager software (RevMan, version 5.3, Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014).

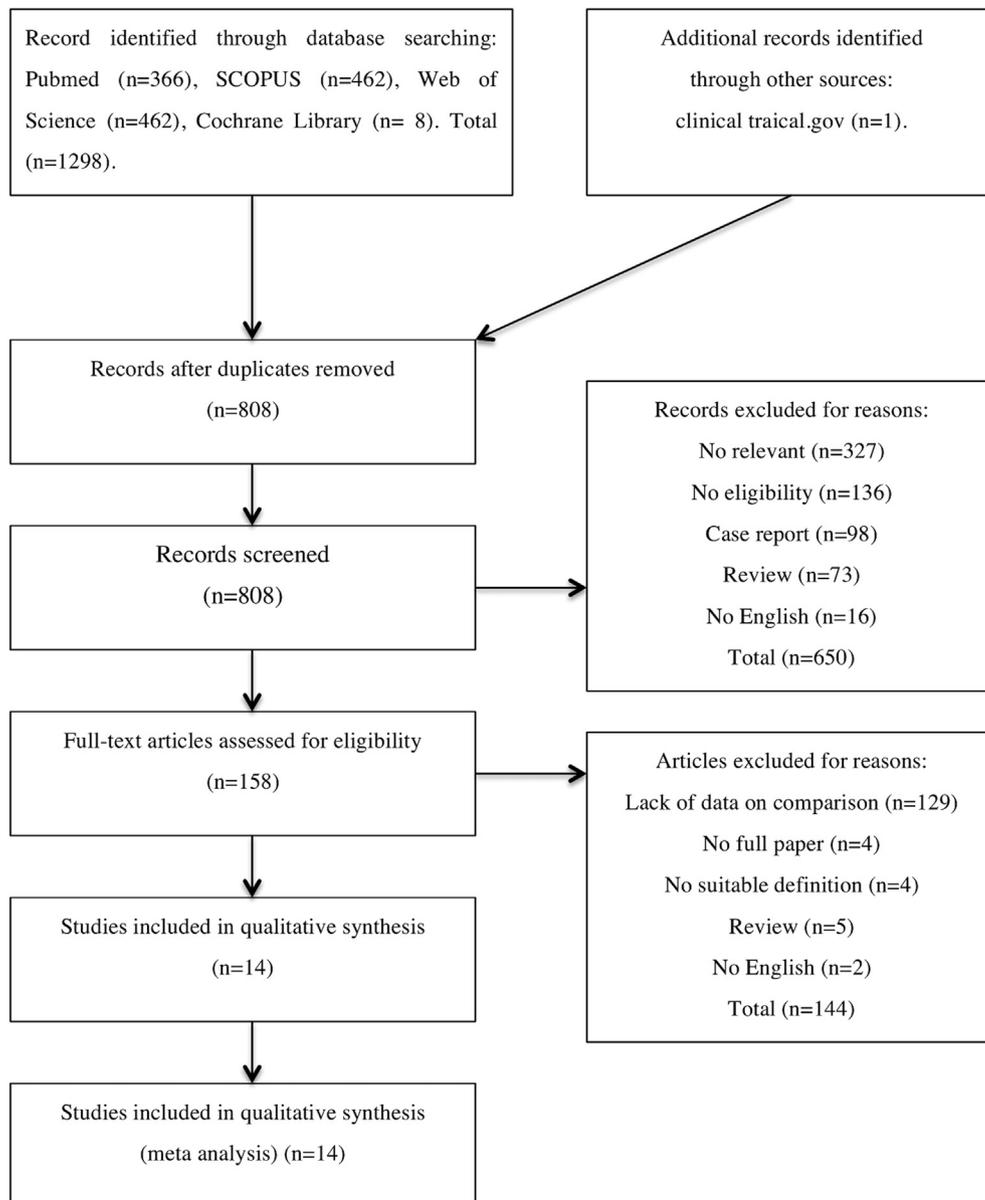
## 3. Results

### 3.1. Selection of relevant studies

The initial database review retrieved 1299 potentially relevant publications. The screening process of relevant studies is depicted in Fig. 1. Full text evaluation was performed in 158 publications after screening the titles and abstracts as described in the methods section. Eighteen full text articles were identified after excluding reviews, conference abstracts, no English articles and articles with lack of data on comparison. After excluding another four publications with inappropriate definitions of SP [5,7,17,18], 14 papers with pooled HRs by multivariate analysis were included in the systematic review and the meta-analysis.

### 3.2. Study characteristics

Table 1 summarizes the main characteristics of the included studies. All studies were based on retrospective data analyses and



**Fig. 1.** Flow chart of the identification of relevant studies.

were published between 2011 and 2017. A total of 12,137 patients with LADC were analyzed; SP subtype was reported in 10.2% ( $n = 1246$ ) of the patients. The majority of studies (93%) were performed in Eastern Asia. Adjusted HRs and 95% CIs for OS and/or DFS were reported directly in all included studies. Gender, age, smoking status, stage, tumor size, nodal status and type of operation were available as potential confounders in all 14 studies and adjusted for in most of them. The quality of included studies was assessed by QUIPS (Table 2).

### 3.3. Meta-analysis of the effect of SP subtype in LADC patients on OS and DFS

In 12 of the 14 included studies (11,811 patients) OS data was available and the pooled estimates showed that SP patients had significantly shorter OS than those without SP subtype (HR 1.44, 95% CI 1.26–1.66) by multivariate analysis, with no significant heterogeneity ( $I^2 = 38\%$ ,  $P = 0.09$ ) (Fig. 2A) [8,17,19–28]. In the 7 of

the 14 included studies (2404 patients) DFS of LADC patients was reported. The pooled HR of 1.27 (95% CI 1.14–1.42) indicated that patients with SP had poor DFS with no significant heterogeneity ( $I^2 = 0\%$ ,  $P = 0.50$ ) [18,19,23,24,27–29] (Figure 2B). The only publication, which failed to show a significant impact of SP subtype on survival was published by Sun et al. in a cohort of exclusively stage I LADC patients (DFS: HR: 1.21, 95% CI, 0.98 to 1.97, OS: HR: 1.22, 95% CI, 0.74 to 2.15) [23].

The funnel plot analysis for OS was symmetrical and concentrated, suggesting that there is little possibility of publication bias for the included publications. (Supplemental material: Fig. 1).

## 4. Discussion

Lung adenocarcinoma is classified into five main histological subtypes with distinct differences in invasiveness, aggressiveness and potential influence on survival [2]. Especially solid predominant LADC has recently been reported to be associated with lymph

**Table 1**  
Characteristics of studies included in the meta-analysis.

First Author (year) <sup>a</sup>	Years included	Country	Patients (No.)	SP <sup>b</sup> (%)	TNM Stage <sup>d</sup>	Stage <sup>e</sup> (%)				Follow-up, Median (month)	L/S/P/B <sup>f</sup> (%)
						I	II	III	IV		
Fujimoto (2017) [17]	2001–2009	Japan	328	20.7	I–III	77.7	11.5	10.7	0	Mean, 45 (range, 0.3–126.8)	NA
Gao (2017) [19]	2011–2014	China	534	18.4	I–III	57.9	10	32.2	0	29	85/3/2/5
Koh (2016) [18]	2005–2009	Korea	230	22.7	I–III	NA	NA	NA	0	52.4 (range, 1–83.7)	NA
Lee (2012) [20]	2005–2009	Korea	110	21.8	I–III	39.1	20	40.9	0	NA	NA
Sakurai (2014) [21]	2010	Japan	6220	1.7	I–IV	72	10	13	4	NA	80/19/1/0
Shimoji (2016) [22]	2007–2009	Japan	165	15.1	I–IV	65	20	15	1	NA	95/NA/NA/NA
Sun (2014) [23]	2002–2011	China	136	10.2	IB	100	0	0	0	74 (range, 21–145)	87/13/0/0
Sun (2015) [29]	2007–2012	China	96	21.9	I–III	44	21	35	0	range, 16.5–69.0	NA
Warth (2015) [24]	2002–2010	Germany	674	36.7	I–IV	39	22	36	3	Mean, 38.2	82/3/13/2
Watanabe (2015) [25]	1998–2007	Japan	2316	11.9	I–IV	82		18		NA	NA
Westaway (2013) [26]	2000–2010	Australia	152	30	I–III	52	28	20	0	33 (range, 0–123)	88/5/7/0
Xu (2017) [27]	2012–2013	China	229	24.2	I–III	NA	NA	NA	0	35.6	NA
Zhang (2014) [8]	2007–2013	China	442	21.2	I–III	56	14	30	0	NA	NA
Zhang (2016) [28]	2007–2010	China	505	23.3	I–III	44	16	40	0	Mean, 43.0 (40.2 ± 17.3)	88/4/3/6

<sup>a</sup> The design of all studies was retrospective. <sup>b</sup> Percentage of patients with solid predominant (SP) subtype. <sup>c</sup> Percentage of patients with solid component (SC). <sup>d</sup> Seventh edition of the tumor-node-metastasis (TNM) staging system. <sup>e</sup> Percentage of patients in each TNM stage. <sup>f</sup> Type of operation; L = Lobectomy, S = Sublobectomy/Segmentectomy, P = Pneumonectomy, B = Bilobectomy. <sup>g</sup> Number of pathologist independently diagnosing. NA = not available.

**Table 2**  
Quality Assessment by QUIPS and Adjusted Confounders for eligible studies.

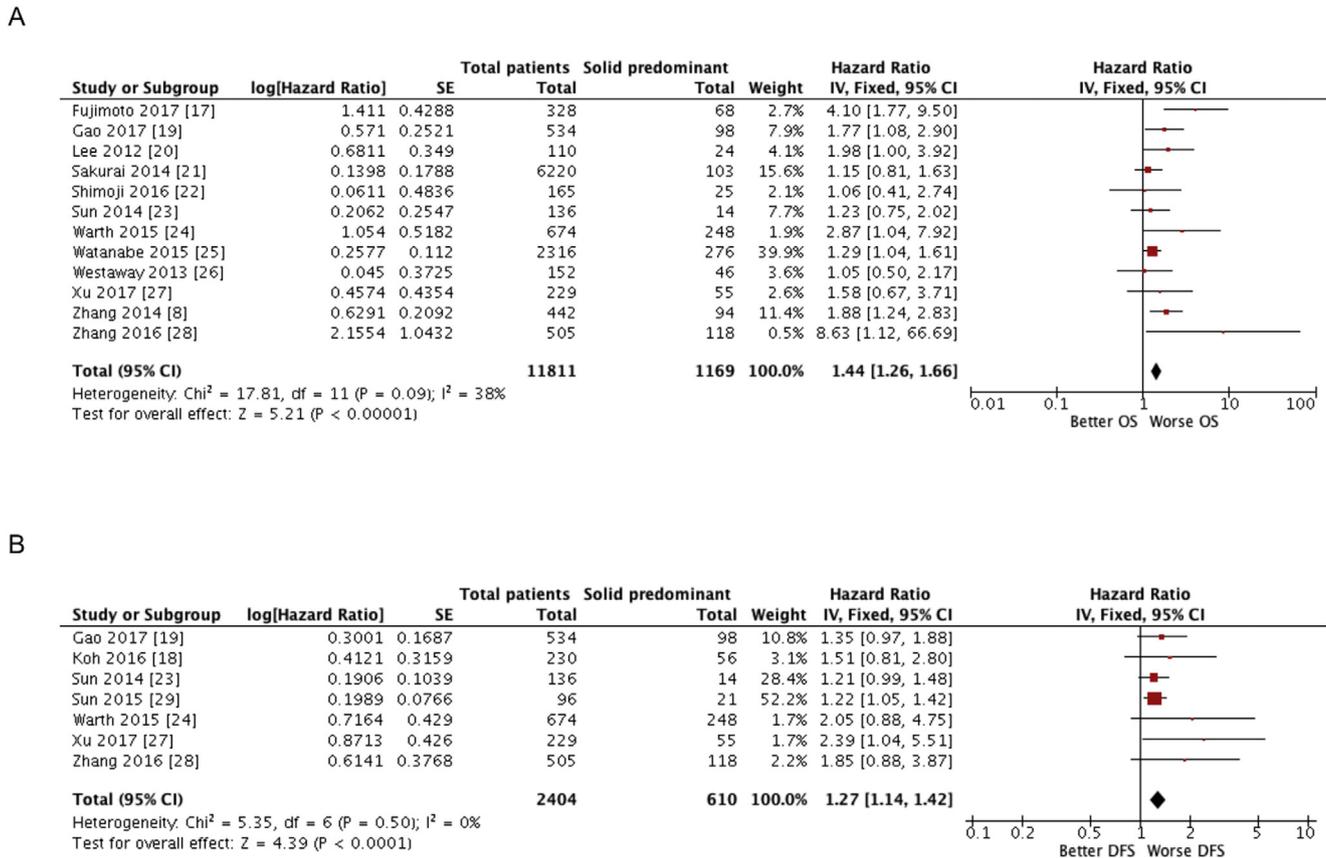
First Author (year)	Study Participation	Study Attrition	Prognosis Factor Measurement	Outcome measurement	Study Counfounding	Statistical Analysis and Reporting	Adjusted Confounder
Fujimoto (2017) [17]	Low	Low	Moderate	Low	Low	Low	TNM Stage <sup>a</sup> (II–III vs. I), Pleural invasion (present vs absent), Lymphatic invasion (present vs absent), Vascular invasion (present vs absent), Tumor grade (poorly differentiated vs well differentiated/moderately differentiated)
Gao (2017) [19]	Low	Low	Low	Low	Low	Low	Age, Sex, Smoking status, Tumor size, T stage, N stage, Adjuvant therapy, Technique
Koh (2016) [18]	Low	Moderate	Moderate	Low	Low	Low	Age, Sex, Smoking status, pT stage, pN stage, LVI <sup>b</sup> , Adjuvant chemotherapy, Presence of micropapillary subtype
Lee (2012) [20]	Unclear	Unclear	Low	Low	Moderate	Low	Nodal metastasis, pTNM stage, Mucinous/enteric variant
Sakurai (2014) [21]	Moderate	Unclear	Low	Low	Low	Moderate	Age (<50 vs 50–70 vs > 75 years), Sex, Smoking status, Tumor size, pT stage, pN stage, Histological subtypes, Surgical curability (Complete vs Incomplete)
Shimoji (2016) [22]	Low	Unclear	Low	Low	Low	Low	Age, Sex, Smoking status, pTNM Stage, Histological subtypes, Type of surgery
Sun (2014) [23]	Low	Low	Low	Low	Low	Low	Age (<65 vs ≥ 65 years), Sex, Smoking status (Never vs Former or current), Tumor size (>3 cm vs ≤ 3 cm), Pleural involvement, Lymphatic and/or vessel invasion, Histological subtype, Adjuvant chemotherapy, Grade (Well vs Moderate or poor)
Sun (2015) [29]	Moderate	Low	Low	Low	Low	Low	Age (>55 vs. ≤ 55 years), Sex, pTNM stage (II–III vs. I), Differentiation (poor vs. well/moderate)
Warth (2015) [24]	Moderate	Low	Low	Low	Moderate	Low	Age, Sex, TNM Stage, Predominant subtypes
Watanabe (2015) [25]	Moderate	Unclear	Low	Low	Low	Moderate	Sex, Tumor size, T stage, Node metastasis, Pleural invasion, Vascular invasion, Lymphatic invasion, Cavity formation, CEA <sup>c</sup> , tumor location, Presence of micropapillary predominant subtype
Westaway (2013) [26]	Low	Moderate	Low	Low	Moderate	Low	Age, Sex, TNM Stage, Adenocarcinoma subtypes
Xu (2017) [27]	Low	Moderate	Low	Low	Low	Low	Tumor size, Node metastasis, Pathologic differentiation
Zhang (2014) [8]	Low	Unclear	Low	Low	Moderate	Low	pTNM stage, LVI, Histological subtypes
Zhang (2016) [28]	Low	Low	Low	Low	Low	Low	Sex, Smoking status, T stage, pN stage, VPI <sup>d</sup> , LVI, Histological subtypes, Type of operation, Differentiation

<sup>a</sup> Seventh edition of the tumor-node-metastasis (TNM) staging system.

<sup>b</sup> Lymphovascular invasion.

<sup>c</sup> Carcinoembryonic antigen.

<sup>d</sup> Visceral Pleural invasion.



**Fig. 2.** Forest plots show adjusted analysis of effects of solid predominant subtype on OS(A) and DFS(B) in all ADC patients after pulmonary resection.(SE=standard error,-CI=Confidence interval.)

node metastasis, vascular and pleural invasion and distant metastases [5,9,17,18,30]. Moreover, SP subtype of LADC is associated with adverse pathological features such as high rates of cellular atypia (72%), moderate/high mitotic activity (100%), extensive tumor necrosis (40%), moderate/strong desmoplasia (72%) and extensive spread through air spaces (STAS) (32%) according to a recent study [31]. Although several cohort studies have consequently reported worse OS associated with SP subtype, these findings have not been yet validated in larger international studies. Thus, the potential impaired prognosis of SP LADC is not yet broadly accepted as an independent prognostic factor in addition to the TNM staging system or implemented into international treatment guidelines. We therefore aimed to summarize all available evidence on the relationship between SP subtype and clinical outcome in LADC patients after surgical resection.

In this systematic review and meta-analysis, 14 studies were analyzed including a total of 12,137 patients treated with surgical resection. To the best of our knowledge, this is the first meta-analysis investigating the impact of SP subtype on survival. Hence, we provide evidence that SP subtype is associated with significantly worse DFS and OS in LADC patients undergoing surgical resection.

Furthermore, almost all studies in this meta-analysis were statistically adjusted for the latest TNM staging system. Our data suggest that the negative prognostic impact of SP subtype on survival is consistent among all stages and independent from the TNM descriptors. However, in one of the included studies [23], patients with stage I SP LADC had a similar prognosis as compared to non-SP patients. Nevertheless, the data generated from our pooled analysis suggests that SP subtype is significantly associated with worse

survival in stage I-IV LADC.

Apart from SP histological subtype, additional pathological tumor features have been previously described to be associated with OS in LADC. Especially, lymphovascular invasion, pleural invasion and micropapillary subtype are known pathologic factors of an unfavorable prognosis in LADC [32–39]. Moreover, the combination of solid and micropapillary subtype in LADC specimens is associated with even worse outcome compared to solid or micropapillary predominant subtype alone [40]. Furthermore, Zhao et al. reported poor OS in patients with solid minor component (SMC, defined as more than 5% but not predominant) in comparison with non-SMC LADC by multivariate analysis (HR: 1.56, 95% CI, 1.26 to 1.94) [7]. However, to date only pleural invasion as a distinct pathological tumor feature has been included in the TNM staging classification [41]. The herein presented data suggests that SP is another pathological discriminator to be included in the next revision of the TNM classification for LADC. Nevertheless, further research is due to determine the optimal combination of anatomical, pathological and molecular features to effectively estimate individual patient prognosis.

Current treatment guidelines recommend adjuvant chemotherapy after complete surgical resection for patients with T1/T2 LADC and N1 lymph node involvement (stage IIB, TNM-8) [42]. However, it is yet under debate, if patients with stage T2a/b N0 tumors might benefit from adjuvant systemic treatment, especially those at higher risk for recurrence with poorly differentiated tumors, vascular or visceral pleural involvement or tumors >4 cm in largest diameter [43,44]. Adjuvant chemotherapy was recently reported to improve DFS in patients with stage IB SP LADC after complete surgical resection [4]. Moreover, a recent study showed

that adjuvant chemotherapy reduces recurrence rates in patients with stage IB LADC of micropapillary or solid predominant subtype [45]. The pooled data of this meta-analysis together with the current literature provide further evidence that patients with pT1/2 pN0 LADC and SP subtype might be candidates for adjuvant chemotherapy after complete surgical resection due to the higher probability of recurrence and worse survival outcome.

The currently preferred treatment of stage I-II LADC is primary surgical resection and lobectomy is accepted as the appropriate type of surgery [42,46]. Several prospective randomized phase III trials are to date investigating whether patients with small (2 cm or less) peripheral NSCLC can safely undergo sublobar resection while maintaining rates of survival and recurrence that are comparable to lobectomy [47]. The final results of these studies are still to be awaited and might define the future role of sublobar resection in stage I LADC, especially in patients with adverse pathological features such as SP subtype. To date, however, sublobar resection cannot be recommended for early stage SP LADC due to the more aggressive features of this tumor entity.

Oncogenic driver mutations in resectable early stage LADC patients have recently emerged as a new potential target of adjuvant treatment to decrease the risk of recurrence and consequently prolong overall survival. Previous studies demonstrated that SP subtype was associated with the following rates of driver mutations: 3.0–36.8% in EGFR, 11.7–44% in ALK, 10.5–30.1% in KRAS, 0–25% in BRAF, 3.8–5.3% in RET and 2.2–21% in ROS1 [48–54]. Among these, ALK rearrangement was significantly more frequent in SP than in non-SP subtype [48,54]. Similarly, the positive rate of programmed death-ligand 1 (PD-L1) was also significantly higher in LADC with SP subtype [55,56]. Several studies are currently investigating the potential role of different tyrosine-kinase inhibitors (TKIs) in the adjuvant setting of completely resected mutation positive stage I-III LADC patients. Final results are yet to be awaited but additional testing of resected LADC by immunohistochemistry and next generation sequencing to assess histological subtype, PD-L1 and mutational status might provide valuable information to guide adjuvant treatment in the near future.

This meta-analysis has several limitations. First, only retrospective cohort studies were available to be included in this review. Therefore, patients with incomplete clinical data were excluded, possibly creating a selection bias. There may be a reporting bias related to the fact that studies not identifying independent predictors of outcomes are less likely to be published. Almost all studies included were published in Eastern Asia. It is currently unknown whether the herein reported assumptions can be extrapolated to other races. Moreover, we have not addressed the potential influence of oncogenic driver mutations. To overcome these limitations, a multicenter prospective approach would be needed to adjust for all of the above-mentioned possible confounders.

## 5. Conclusion

SP subtype in LADC is associated with significantly worse OS and DFS in all stage patients undergoing pulmonary resection. This study provides evidence that distinct histological LADC subtyping represents a strong prognostic factor and may be implemented into prognostic tools to estimate individual patient prognosis and into guidelines for adjuvant treatment in completely resected T2a/b N0 LADC.

## Meeting presentation

None.

## Conflict of interest

No conflict of interest disclosures from any authors.

## Disclosure

All authors have no conflicts of interest or financial ties to disclose.

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## Appendix A. Supplementary data

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