A new prognostic index model using meta-analysis in early-stage epithelial ovarian cancer

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A new prognostic index model using meta-analysis in early-stage epithelial ovarian cancer

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This certifies that the Master's Thesis
of Hyun Jong Park is approved.

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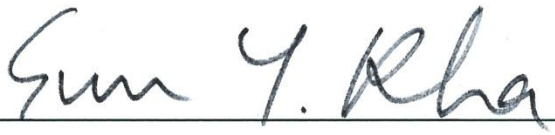

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Sincerely,

Hyun Jong Park

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ABSTRACT

A new prognostic index model using meta-analysis in early-stage epithelial ovarian cancer

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Objectives: To construct a novel prognostic index (PI) model of early-stage epithelial ovarian cancer (EOC).

Methods: The PI model was constructed through meta-analyses. The methodological quality of the studies was assessed using the modified Jadad scale for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for non-RCTs. The prognostic factors of the PI model that had a significant impact on the recurrence-free survival (RFS) of patients with early-stage

ovarian cancer were chosen. A total of 177 patients with early-stage ovarian cancer who were treated at Severance Hospital from January 1999 to September 2011 were analyzed using the new PI model to test its utility.

Results: The equation PI = 2 × age + 86 (if grade 2) or 105 (if grade 3) + 53 (if stage Ib or Ic) or 130 (if stage II) + 53 (if no lymphadenectomy) - 43 (for adjuvant chemotherapy of 3 times or more) + 10 (calibrating constant) was derived. Based on PI values, the high-risk group showed a significant 5 year-RFS difference compared to the low-risk group (*P*-value <0.01 by log-rank test) and a borderline significance in comparison to the intermediate-risk group (*P*-value=0.08). When the cutoff level of PI values was set at 211, the low- and high-risk groups of recurrence within 5 years were also identified by Cox regression analysis (HR=7.25, 95% CI: 2.98-17.65) .

Conclusions: Our PI model was predictive in this study and may be effective in clinical practice. Further prospective studies should be conducted to confirm the predictive ability of the new PI model for early-stage EOC recurrence.

Keywords: meta-analysis, early-stage ovarian cancer, recurrence, prognostic index, prognosis factor, prediction

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I. INTRODUCTION

Among the cancers that exclusively affect females, ovarian cancer is the leading cause of death in females across the world.[1] Of all epithelial ovarian cancer (EOC) patients, only 25% are diagnosed as early-stage EOC.[2] The 5-year survival rate of early-stage EOC varies from 50 to 85%.[3] It is important to accurately predict the prognosis in ovarian cancer. Making the prognostic index (PI) allows a precise analysis by stratifying the patients, and an individual treatment according to prognosis.[4,5]

In cases of advanced stage EOC, low survival and a high recurrence risk energized efforts to develop a PI model for more accurate prognosis predictions.[4-6] The research method for establishing a PI model involves collecting a sufficient size of samples and developing the reliability of hazard ratio (HR) for survival for each prognosis factor. However, considering the low diagnosis frequency of early-stage EOC, it may be difficult to find a HR with high reliability.

To obtain a HR with a high reliability for prognosis factors in such instances, the use of meta-analysis is a viable alternative. After evaluating the quality of the literature, high quality data can be used to obtain the overall estimate of treatment effects or HRs.[7]

The authors intend to propose a new PI model for recurrence prediction by performing meta-analyses on prognosis factors influencing recurrence after primary treatment against EOC of FIGO stage I and II.

II. MATERIALS AND METHODS

1. Meta-analysis

A. Primary endpoint

Overall survival (OS) is the optimal endpoint of clinical study; however, this requires a substantial timeframe of measurement and also a vast sample size. For diseases with low frequency and prevalence, recurrence-free survival (RFS) is a more suitable endpoint in prognosis measurements than OS.[8,9] This study targeted early-stage EOC with low onset frequency, and thus a significant hazard ratio of the prognostic index for RFS and not OS was taken as the primary endpoint for a more sensitive prognosis measurement.

B. Literature search

Literature search was performed using the keywords, "ovarian cancer", "early stage", "prognosis", "prognostic factor" and "recurrence" in MEDLINE (from January 1998), SCOPUS (from May 1994) and Cochrane library (from January 1985) for articles published till August 31, 2011. The study subjects included patients with early-stage ovarian cancer (FIGO stage I-II), and studies with titles and abstracts containing sufficient information which could be used for meta-analysis were considered for inclusion in this study.

C. Study selection

The patients from the literature that were to be included in our meta-analyses were those with a histologically confirmed diagnosis of early-stage ovarian cancer via surgery. Regarding EOC patients of FIGO stage I or II, papers that clearly suggested the hazard ratio of prognostic factors for RFS after primary treatment (surgery and/or postoperative adjuvant chemotherapy) were included in meta-analyses (hazard ratio was limited to the values suggested by multivariate analysis and not univariate analysis.[6] The papers which suggested only the resources for OS were excluded. According to titles and abstracts, literatures with subjects different from the research objective, those written in languages other than English, and those whose original full text could not be confirmed were also excluded from our study. The publication year, authors, study centers, and study periods were investigated, and overlapping articles were excluded. Also, through the quality assessment method of the literature proposed below, only the resources considered to be of high quality were selected as the target of meta-analysis.

D. Methodological quality assessment

The objective of this paper was to first find the pooled hazard ratio using meta-analysis, and then to propose a prognostic index model based thereon. Not only randomized controlled trials (RCTs) but also non-RCTs were included in our meta-

analyses. To evaluate the quality of the papers, the modified Jadad scale (6-items, total 8 scores) for RCTs and the Newcastle-Ottawa scale (NOS) was used for non-RCTs. All papers were independently assessed by two reviewers (Park HJ and Kim YT) and papers graded with more than 4 stars on the NOS or more than 4 scores on the modified Jadad scale were considered to be of high quality.[10,11] Any discordance in the opinion between the reviewers was solved through discussion and agreement.

RFS was defined as the time after the primary treatment of EOC until relapse. The prognosis factors of each study that were proposed as affecting RFS, i.e., postoperative adjuvant chemotherapy, FIGO stage, histologic cell type, tumor grade, age, optimal staging procedure execution and such, were investigated for the hazard ratio. Using the aforementioned inclusion and exclusion criteria, two independent reviewers (Park HJ and Kim YT) executed data extraction, and again any discrepancy between the reviewers was resolved through discussion and agreement.

E. Data analysis

Data were analyzed using the Comprehensive Meta-Analysis version 2.0 software (Biostat, USA). The results of this study were expressed as a pooled hazard ratio (HR) and 95% confidential intervals (CI). Study-to-study variation was assessed using the Higgins I^2 test, which measured the proportion of the total variation across studies. When significant heterogeneity (P-value ≤ 0.1 or $I^2 \geq 50\%$) was not observed between

the subgroups in the meta-analysis, the fixed effects model (the inverse variance method) was used, and when significant heterogeneity was observed, the random effects model (DerSimonian and Laird methods) was used.

2. Prognostic index model

Our analyses were made based on the original publications and not on a patient database.

If a pooled hazard ratio for each prognosis factor was found through meta-analysis, the regression coefficient, drawn by applying a regression function to the pooled hazard ratio could be expressed as the weight value for each prognosis factor. That is, the prognostic index could be expressed in the following formula.

$$\textbf{PI formula} = \alpha_1 X_1 + \alpha_2 X_2 + \cdots + \alpha_n X_n$$

Here, X was the prognosis factor significantly affecting RFS on meta-analysis, and α was the regression coefficient for the pooled hazard ratio.

After applying this "formula for PI" to 177 patients diagnosed with early-stage ovarian cancer and treated at Severance Hospital within the period of January 1999 to September 2011, the patients were divided into three groups according to the distribution of their PI values. The plan was to execute survival analysis for RFS through Kaplan-Meier methods and thus to evaluate the significance in recurrence prediction of early-stage ovarian cancer according to the PI value (We made reference

to articles about prognostic index model.[6,12]). In addition, the PI value to maximize sensitivity and specificity was found with respect to the occurrence of recurrence in 177 patients. Based on the PI value, patients were divided into two groups (high-risk and low-risk groups) and Cox regression test was executed, which was the method to obtain the cutoff PI value to maximize the hazard ratio in RFS for recurrence prediction. The SPSS software version 14.0 (Chicago, USA) was used for survival analysis, and *P*-values < 0.05 were considered statistically significant.

III. Results

1. Meta-analysis

In this study, we ultimately enrolled 10 studies[13-22] (Figure 1). Among them, two[17,18] substantially overlapped in study organization and period, but there was no overlap in the description of the results, so both were enrolled in the present study. Some of the studies were RCTs[13,14,16-19] and some were observational studies.[15,20-22] The methodological qualities of the studies included in our meta-analyses are summarized in Table 1. As results of the evaluation of the quality of the literature, two studies[20,22] showed weak ground levels and thus were excluded from our meta-analyses.

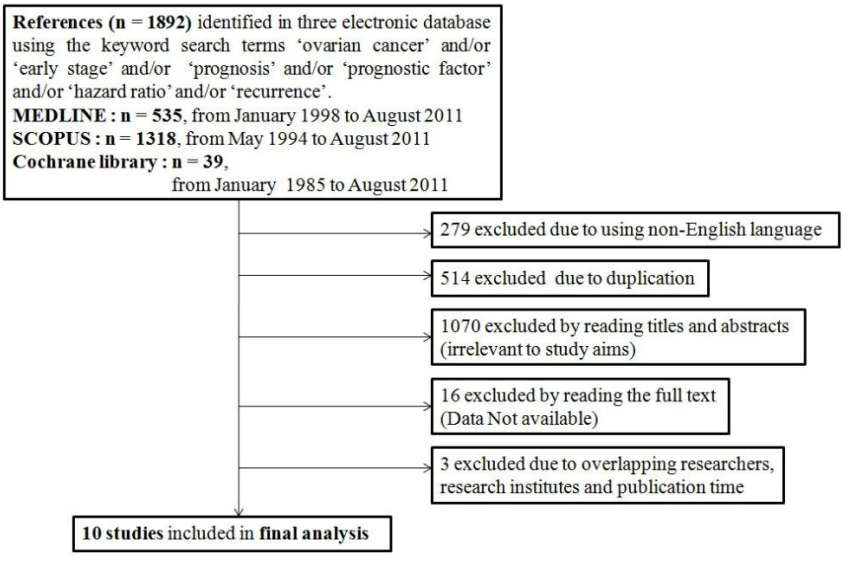

Figure 1. Flow chart of study selection.

Table 1. The results and the methodological qualities of selected studies

Study	Patients	Recruitment period	Study type	Primary comparison	Methodologic quality assessment
Bolis (1995)	n = 85, Stage Ia-Ib, Grade 2-3	1983-1990	RCT	POAC vs Observation (cisplatin 50mg/BSA, 6cycles)	mJad: 6 (high)
Trope (2000)	n = 175, Stage I (100%)	1992~1997	Multicenter RCT	POAC vs Observation (carboplatin AUC7, 6 cycles)	mJad: 5 (high)
Vergote (2001)	n = 1545, Stage I (100%) POAC – not stated	1971~1998	Multicenter retrospective cohort study	Evaluation of prognostic factors	NOS: 5 stars (high)
ACTION (2003)	n = 448, Stage I-IIa (Stage I: 92.6%)	1990~2000	Multicenter RCT	POAC vs Observation (cisplatin 75 or carboplatin 350 mg/m^2, 4~6 cycles)	mJad: 5 (high)
ICON1 (2003)	n = 477, Stage I-III (stage I-II: 97.5%).	1991~2000.	Multicenter RCT	POAC vs Observation (single agent carboplatin AUC 5 or CAP regimen, 85% 6cycles)	mJad: 5 (high)
Maggioni (2006)	n = 268, Stage I-II (Stage I: 70%), POAC 61%	1991~2003	Multicenter RCT	Evaluation of systemic lymphadenectomy	mJad: 5 (high)

Chan (2008) (including GOG95 & GOG157 studies)	n = 506, Stage I-II (Stage I: 68.6 %), POAC 100%	GOG 95: 1995~1998 GOG 157: 1986~1994	Analysis of two multicenter RCTs	Evaluation of prognostic factors	GOG 95 - mJad: 4 (high) GOG 157 - mJad: 6 (high)
Kang (2010)	n = 95, Stage I-II (Stage I: 62.1%), POAC 100%	1998~2004	Single center retrospective cohort study	Evaluation of prognostic factors	NOS : 2 stars (low)
Bamias (2011)	n = 147, Stage I-II (Stage I: 88.4%) POAC 100%	1996~2005	Single center retrospective cohort study	Evaluation of prognostic factors	NOS : 3 stars (low)
Skirnisdottir (2011)	n = 131, Stage I-II (Stage I: 84.7%)	2000~2004	Multicenter prospective cohort study	Prognostic effects of p53, p27 and C-myc	NOS : 5 stars (high)

POAC, postoperative adjuvant chemotherapy; RCT, randomized controlled clinical trial; mJad, the modified Jadad scale; NOS, Newcastle–Ottawa scale.

The results of intervention effects for hazard ratios, as proposed in these studies, were as follows.

For tumor grade of clear cell carcinoma, based on the references[14,23,24] that it reflects a bad prognosis beyond poor differentiation, it was included in grade 3. As the result of a fixed effects model (I^2=0.0%), tumor grade 2 demonstrated a significant hazard ratio (HR) compared to grade 1 in terms of RFS (HR=2.37, 95% CI; 1.62-3.48) (Figure 2-A). As for tumor grade 3, a random effects model was applied (I^2=77.8%), demonstrating a significant HR of about 2.87 times that of grade 1 (HR=2.87, 95% CI; 1.73-4.75) (Figure 2-B).

The literature review of FIGO substage was as follows. The result of multivariate analysis comparing stage Ia and stage Ib was only suggested in the study of Vergote et al.[15], and stage Ib was found to show a significant HR in RFS of 1.70 times that of stage Ia (HR=1.70, 95% CI; 1.01-2.85). Considering the reports by Vergote et al.[15] and Chan et al.[19], there was no significant difference between stage Ic and stage Ia-Ib, and thus stage Ic and stage Ib were assumed to show the same HR. As for stage II, the fixed effects model was applied (I^2=0.0 %), and as a result, it showed a significantly higher HR of 2.16 times that of stage I (HR=2.16, 95% CI; 1.59-2.93) (Figure 2-C). However, stage I here included all stages of Ia, Ib, Ic, so correction of the above HR was inevitable. This study assumed the situation with maximized risk to determine the HR. Therefore, the final HR of stage II took stage Ia as reference, and was processed as the multiple

of stage Ib and the aforementioned pooled HR. The final HR of stage II was determined to be 3.67 (reference: stage Ia).

According to the study of Chan et al.[19], those over 60 years of age upon multivariate analysis have been reported to show a significant HR compared to those below 60 years (HR=1.57, 95% CI; 1.12-2.19). Also in the large-scale multi-institutional retrospective study[15], One year increase in age led to a significant increase (1.02 times) in HR (HR=1.02, 95% CI; 1.00-1.03). In this study,while other prognosis factors were categorical variables, age was the only consecutive variable, so it was decided that the results of Vergote et al.'s study[15] regarding age were to be used intact.

Inadequate staging where lymphadenectomy was not executed had a significantly higher risk for recurrence of about 1.69 times that of an optimal staging procedure including lymphadenectomy (HR=1.69, 95% CI; 1.23-2.33) (Figure 2-D). Also, cases with postoperative adjuvant chemotherapy of 3 cycles or more showed significant HR of 0.65 times that of cases with observation (HR=0.65, 95% CI; 0.52-0.82) (Figure 2-E).

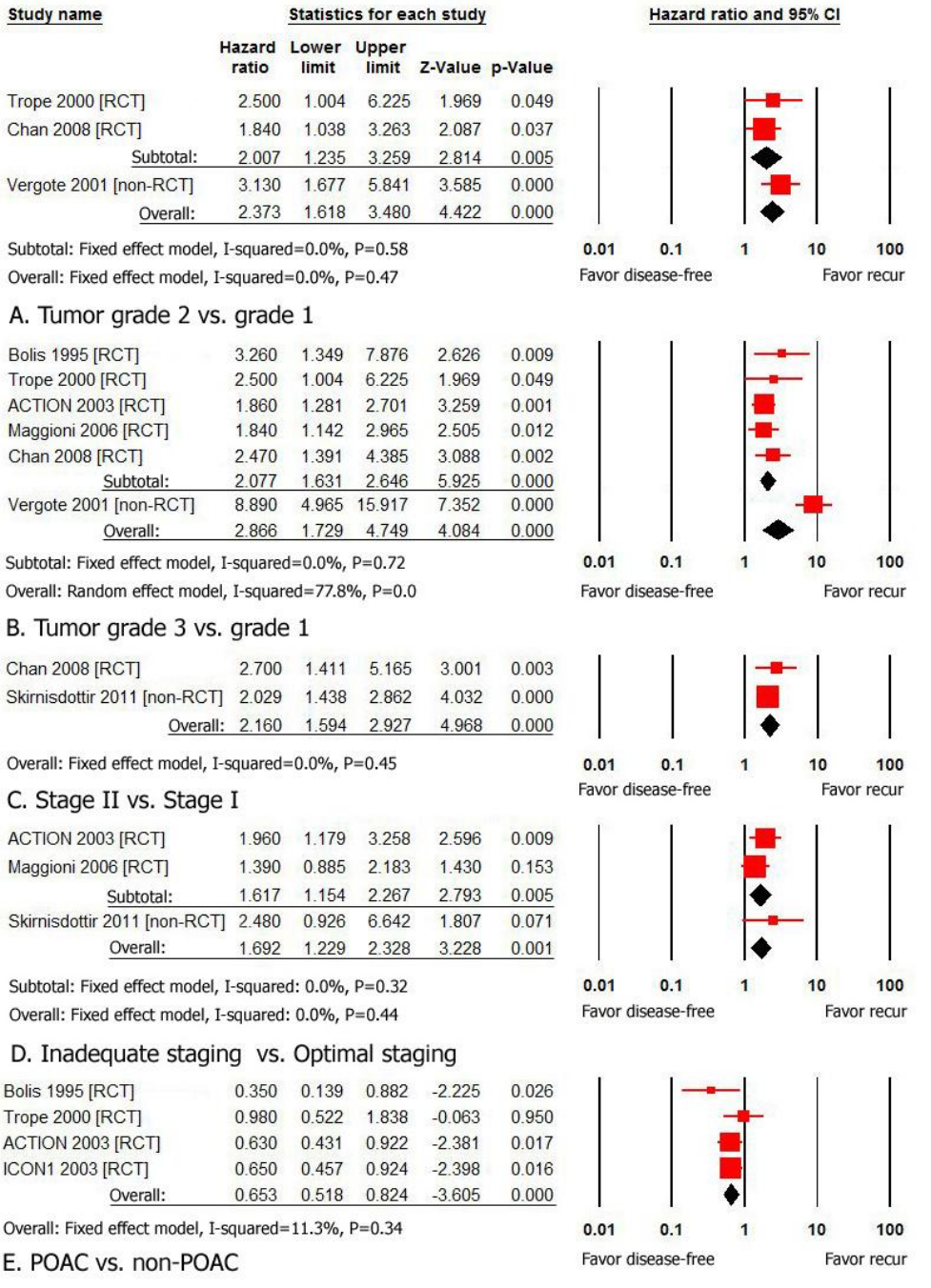

Figure 2. Forest plots illustrate the results of the meta-analyses. The intervention results of the hazard ratios for recurrence-free survival for tumor grade (A, B),

stages I–II (C), inadequate staging procedure (D), postoperative adjuvant chemotherapy (E). Horizontal lines represent 95% confidence intervals.

In cases of histologic cell type, it is the predominant conclusion that the results of related references[15,16,21] shows insignificant HR in RFS, and thus this paper concluded that the influence of histologic cell type recurrence on early-stage EOC was not significant.

2. Application of the prognostic index model

After finding the regression coefficient for each of the pooled HR above, the PI formula was proposed as follows.

PI formula = 2 × age + 86 (if grade 2) + 105 (if grade 3) + 53 (if stage Ib or Ic) + 130 (if stage II) + 53 (if no lymphadenectomy) – 43 (for adjuvant CTx of 3 times or more) + 10 (calibrating constant)

The clinical characteristics of the 177 patients to which the PI formula was applied are listed in Table 2. Twenty-five patients did not undergo the postoperative adjuvant therapy, and adjuvant radiotherapy was not performed at all in 177 patients. Their median PI value was 205 (range: 3~402).

Table 2. Characteristics of 177 patients from Severance Hospital

Age (median, range, years)	47 (17-79)
Follow-up periods (median, range, months)	35 (3-143)
Surgical staging performance (n, %)	
Lymphadenectomy (complete staging)	152 (85.9)
No lymphadenectomy (inadequate staging)	25 (14.1)
Postoperative adjuvant chemotherapy (n, %)	
Less than three times	28 (15.8)
No Chemotherapy	25
Once	1
Twice	2
More or three times	149 (84.2)
Three times	6
Four times	42
Five times	6
Six times	95
Stage (n, %)	
Stage Ia	55 (31.1)
Stage Ib	2 (1.1)
Stage Ic	80 (45.2)
Stage II	40 (22.6)
Histologic cell type (n, %)	
Serous	65 (36.7)
Mucinous	47 (26.6)
Endometrioid	22 (12.4)
Clear cell	38 (21.5)
Others	5 (2.8)
Histologic grade (n, %)	
1	54 (30.5)
2	45 (25.4)
3 (or clear cell)	78 (44.1)

A PI value below 134 was set for inclusion in the low-risk group (n=42), PI value of 135~268 for the intermediate-risk group (n=98), and a PI value over 269 for the high-risk group (n=37), and then Kaplan-Meier survival analysis (by log-rank test) between the three groups was executed. The high-risk group demonstrated a significant 5 year-RFS difference compared to the low-risk group (5 year-RFS; 60.5 vs 91.0 %, *P*-value <0.01). Also, the high-risk group demonstrated a 5 year-RFS difference with borderline significance in comparison to the intermediate-risk group (5 year-RFS; 60.5 vs 76.6 %, *P*-value=0.08) (Figure 3-A). There was no 5 year-RFS difference between the intermediate-risk group and the low-risk group (*P*-value=0.11). With the PI value of 211 as the cutoff, all of the subjects were divided into two groups and Cox regression analysis was executed. As a result, the group with a PI value over 211 (n=77) showed a significantly greater risk of recurrence within 5 years, which was about 7.25 times that of the group with a PI value below 211 (n=100) (HR=7.25, 95% CI; 2.98-17.65).

When the variable of postoperative adjuvant chemotherapy and calibrating constant were excluded from the above PI formula, the median PI value of the 177 patients was 234 (range 36-402). After reassigning patients with a PI value below 158 to the low-risk group (n=44), 159~280 to the intermediate-risk group (n=89), and over 281 to the high-risk group (n=44), Kaplan-Meier survival analysis (by log-rank test) was executed, resulting in a significant difference in 5 year-RFS between the high-risk group and the low-risk group (5 year-RFS; 62.3 vs 88.7%, *P*-value=0.01). Also, the high-risk group and the intermediate-risk group demonstrated a difference with

borderline significance (62.3 vs 77.5%, *P*-value=0.06). Between the low-risk group and the intermediate-risk group no significant difference of 5 year-RFS was discovered (*P*-value=0.23) (Figure 3-B). With the cutoff value of 243, all of the subjects were divided into two groups and Cox regression analysis was executed. As a result, the group with a PI value above 243 (n=73) had a significantly higher risk for recurrence within 5 years of 4.57 times that of subjects in the group with a PI value below 243 (HR=4.57, 95% CI; 2.11-9.90).

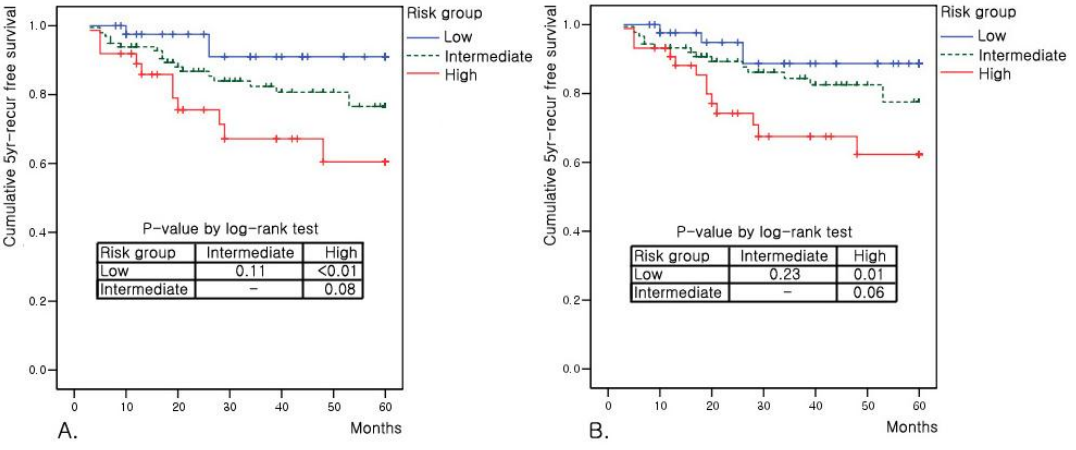

Figure 3. Survival curves according to risk group based on (A) the prognostic index formula and (B) the modified prognostic index formula (when the variable of postoperative adjuvant chemotherapy was excluded from the prognostic index formula).

IV. DISCUSSION

In our study, five factors (age, tumor grade, FIGO stage, optimal staging including lymphadenectomy, postoperative adjuvant chemotherapy) were selected as independent prognosis factors. It is the dominant opinion so far that CA125 does not reflect the prognosis for recurrence in early-stage EOC, so CA125 was not utilized as a prognosis factor in our study.[20,25-27] Histologic cell type was not included in the PI formula as well, because its prognostic value to early-stage EOC was unclear in the literature review.[15,16,21,28-32]

Our PI model could predict the prognosis of patients with early-stage EOC. After ruling out 25 patients who did not undergo lymphadenectomy, we performed a survival analysis among low-, intermediate- and high-risk groups according to PI criteria in our study, which showed that the high-risk group demonstrated a significant 5 year-RFS difference compared to the low-risk group (5 year-RFS; 92.5 vs 68.5 %, P-value=0.023). This fact indicated that our PI model could have the significant capability to predict prognosis of patients despite the conservative assumption that all patients without lymphadenectomy had advanced-stage diseases.

As all the resources used in our study targeted against Western people, the issue of ethnic factors of whether these research results can be applied to Koreans needs to be addressed. Chan et al. and Redaniel et al. reported that the difference in access to

health care would have a more important influence on the survival of ovarian cancer than differences in demographic genetics.[33,34] The 5-year survival of ovarian cancer patients did not show a significant difference per ethnicity in the meta-analysis performed by Terplan et al.[35] Accordingly, it appears as though there is no big problem in applying the meta-analysis results from Western patient to Koreans.

The limitation of this study is that our meta-analyses included non-RCTs and RCTs which were different in study design. The risk of bias in non-RCTs is higher than in RCTs. Especially, in case where the variables of non-RCTs included in our meta-analyses vary, it would be unreasonable to integrate the result values.[36,37] However, it does not imply that meta-analysis cannot be executed at all, and eventually the meaning of the result values integrated by meta-analysis becomes limited. As all result values of RCTs and non-RCTs used in our study were obtained by multivariate Cox regression analysis only, they might be sufficiently compensated for the influence of other variables.[38] In addition, most result values of non-RCTs had the homogeneity similar to those of other RCTs in our study, and Vergote et al.'s study with sample size of 1545 took up the largest portion among subjects. Therefore, it would be possible to acknowledge the legitimacy of our meta-analyses integrating the results of RCTs and non-RCTs.

RCTs including highly selected patient populations and strict research designs do not always reflect actual clinical pactice, and the meta-analysis based solely on RCTs could make false inferences because of the paucity of RCTs.[39-42] Shrier et al. reported

that the advantage of including both RCTs and well-designed observatinal studies in a meta-analysis could outweigh the disadvantage.[43] In addition, the purpose of our study is suggesting a hypothesis rather than proofing the fact. Thus, more flexible criteria could be applied rather than those of a typical meta-analysis which is intended only for RCTs. Anyway, due to paucity of studies included in our meta-analyses, the above limitation may be raised, and therefore the correction of our PI model would be sufficiently possible by future additional researches.

V. CONCLUSION

In conclusion, the PI formula proposed in this study was able to distinguish high-risk and low-risk groups for recurrence of early-stage EOC allowing it to be an important resource for the selection of appropriate treatment options for patients according to recurrence risk (for example, decisions on the scope of primary treatment including adjuvant chemotherapy and the follow-up method). In the future, through a large-scale multi-institutional study, the utility and applicability of the PI formula hypothetically proposed in this report should be further studied.

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ABSTRACT (in Korean)

초기 병기 상피성 난소암에서 메타분석을 이용한 새로운 예후지표 모델의 제시

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목적: 초기 병기 상피성 난소암 환자들에서 정확한 예후 예측을 위한 새로운 예후지표 모델을 구축하기 위함이다.

방법: 본 연구에서 예후지표 모델의 구축을 위해 메타분석을 이용하고자 하였다. 메타분석시 문헌의 방법론적 질평가에 있어서는, 무작위 배정 임상시험들의 경우 수정된 Jadad 척도를, 관찰연구들의 경우 Newcastle-Ottawa 척도를 사용하였다. 예후지표모델에서 이용

된 예후인자들의 경우, 초기 병기 상피성 난소암환자들의 무병생존율 (recurrence-free survival)에 있어서 유의한 영향을 끼치는 인자들만을 선택하였다. 이렇게 하여 만들어진 예후지표모델의 유용성을 확인하기 위해, 세브란스 병원에서 진단 및 치료를 시행한 초기 병기 상피성 난소암 환자 177명에게 적용하여 분석하였다.

결과: "예후지표모델방정식 = 2×나이 + 86(종양등급2의 경우) 또는 105(종양등급3의 경우) + 53(병기 Ib 또는 Ic의 경우) 또는 130(병기 II의 경우) + 53(림프절절제술 시행 안한 경우) - 43(3회이상의 수술후 부가적 항암요법을 시행한 경우) + 10(보정계수)"이 도출되었다. 이 방정식에 의한 값들에 근거하여, 고위험군, 중간위험군, 저위험군을 나눌 때, 고위험군의 경우 저위험군에 비해 5년 무병생존율의 유의한 차이를 보였으며(P-value<0.01 by log-rank test), 중간위험군과 비교할 때는 경계적으로 유의한 차이를 보였다(P-value=0.08). 또한 예후지표값 211을 기준으로 하였을 때, 211이상의 고위험군은 211미만의 저위험군에 비해 5년이내 재발할 위험성이 7.25배로 유의하게 높음을 확인할 수 있었다(Hazard ratio=7.25, 95%신뢰구간: 2.98-17.65).

결론: 본 연구에서 제시한 예후지표모델은 초기병기 상피성 난소암 환자들의 재발을 예측할 수 있었고, 실제 임상에서도 매우 유용하게 이용될 수 있을 것으로 사료된다. 초기병기 상피성 난소암 환자들에서 새로운 예후지표모델의 재발예측능력을 평가하기 위해서는 향후 더 많은 전향적인 연구들이 수행되어야 할 것으로 보인다.

핵심되는 말: 메타분석, 초기병기 난소암, 재발, 예후지표, 예후인자, 예측