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CCNE1 EXPRESSION AND CA-125 LEVELS IN HIGH GRADE SEROUS CARCINOMA OVARY AT MOHAMMAD HOESIN GENERAL HOSPITAL PALEMBANG ; A SINGLE-INSTITUTION DESCRIPTIVE STUDY

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ABSTRAK

High grade serous carcinoma (HGSC) ovarium merupakan subtipe dominan yang menyebabkan kematian akibat kanker ovarium. Amplifikasi CCNE1 terjadi pada 20% HGSC ovarium dan dikaitkan dengan kekambuhan setelah kemoterapi platinum. Penilaian ekspresi CCNE1 dapat menjadi skrining untuk amplifikasi CCNE1. Pengukuran kadar CA-125 secara rutin digunakan untuk pemantauan pengobatan dan kekambuhan pasien HGSC. Penelitian ini bertujuan untuk menilai ekspresi CCNE1, karakteristik demografi, dan kadar CA-125 pasien HGSC ovarium. Dari 31 pasien HGSC, subjek penelitian didominasi oleh pasien berusia >50 tahun (61,3%), stadium klinis FIGO III (64,5%), overexpression CCNE1 (71%), kadar CA-125 praoperasi ≥500 U/ml (77,4%) dan kadar CA-125 pascakemoterapi <35 U/ml (58,1%).

ABSTRACT

CCNE1 Expression in High Grade Serous Carcinoma Ovary at Mohammad Hoesin Genaral Hospital Palembang; A Single-Institution Descriptive Study. High grade serous carcinoma (HGSC) of the ovary is the dominant subtype causing death from ovarian cancer. CCNE1 amplification occurs in 20% of ovarian HGSC and is associated with recurrence after platinum chemotherapy. Assessment of CCNE1 expression can be a screening for CCNE1 amplification. Measurement of CA-125 levels is routinely used for treatment monitoring and recurrence of HGSC patients. This study aims to assess CCNE1 expression, demographic characteristics and CA-125 levels of ovarian HGSC patients. Of the 31 HGSC patients, the study subjects were dominated by patients aged >50 years (61.3%), clinical stage FIGO III (64.5%), CCNE1 overexpression (71%), preoperative CA-125 levels ≥500 U/ml (77.4%) and postchemotherapy CA-125 levels <35 U/ml (58.1%).

INTRODUCTION

Ovarian cancer is one of the most common gynecologic malignancies with a high mortality rate. The number of ovarian cancer deaths in women is the highest after breast cancer and cervical cancer.[1] More than 90% of ovarian cancers are carcinomas, and high grade serous carcinoma (HGSC) of the ovary is by far the dominant subtype that accounts for 70-80% of deaths from all types of ovarian cancer.[2] In Indonesia, based on GLOBOCAN data in 2020, ovarian cancer is ranked third as the cause of cancer deaths in women. There were 15,150 ovarian cancer deaths in Indonesia in 2020.[3]

Epidemiologically, HGSC can be found in a wide age range; most of them are advanced. Research by Kang et all found that CCNE1 amplification tends to be found in older patients.[4] About 80% of HGSC patients are diagnosed in FIGO stage III or IV conditions. The 5-year survival of HGSC patients in early FIGO stages (I and II) can reach 100%. However, in advanced stages (III and IV) the survival of HGSC patients decreases to 33-54%.[5]

High grade serous ovarian carcinoma (HGSC) is characterized by high intratumor heterogeneity. At the molecular level HGSC is characterized by TP53 mutations (96%) and the presence of high chromosomal instability. One of the most frequent causes of chromosomal instability in HGSC is CCNE1 amplification which is found in 20% of ovarian HGSC.[6,7] The CCNE1 gene is located at chromosome locus 19q12 and plays a role in encoding the CCNE1 or cyclin E1 protein which is important in cell cycle regulation.[8] The presence of CCNE1 amplification in HGSC disease is associated with worse prognosis and platinum chemotherapy resistance in HGSC.[9] Stronach et al. found that CCNE1 amplification was associated with decreased OS and PFS in HGSC patients.[10] Another study by Da Costa et al found that CCNE1 amplification was associated with lower platinum treatment response.[11] Target therapy on CCNE1 amplification is the most studied study in ovarian HGSC.[8] Several studies on target therapy using WEE kinase and CDK2 inhibitors are currently in clinical trials.[12]

Cancer Antigen-125 (CA-125) is a form of transmembrane mucin secretion that acts as a biomarker to assess the prognosis and therapeutic response of ovarian HGSC patients. Batchman et al found that OS and PFS will decrease significantly if preoperative CA-125 levels are≥ 500 U/ml.[13] After platinum chemotherapy, CA-125 levels >35 U/ml are significantly associated with the risk of recurrence.[14]

The wide use of immunohistochemical examination in HER2 amplification screening has encouraged the development of CCNE1 immunohistochemistry to predict CCNE1 amplification. Research by Chan et al found that immunohistochemistry can be used to screen for CCNE1 amplification in HGSC with CCNE1 overexpression.[15] Research on CCNE1 expression in ovarian HGSC in Indonesia is still very limited. For this reason, this study aims to assess CCNE1 expression in ovarian HGSC in the Anatomical Pathology Laboratory of FK UNSRI/Mohammad Hoesin General Hospital Palembang. This study also aimed to assess the distribution of HGSC patients based on age, clinical stage of FIGO, preoperative CA-125 and CA-125 levels after platinum chemotherapy. The results of the study are expected to provide understanding and knowledge about CCNE1 expression and characteristics of ovarian HGSC patients, especially at the Mohammad Hoesin General Hospital Palembang.

METHODS

Study design

This study was a descriptive study with a retrospective design conducted at the Anatomical Pathology Laboratory of the Faculty of Medicine, Sriwijaya University/Mohammad Hoesin General Hospital Palembang. The study population was all patients with ovarian removal diagnosed with histopathologic ovarian HGSC from January 1, 2020 to May 31, 2024 who met the inclusion criteria and exclusion criteria. Inclusion criteria include archived preparations and paraffin blocks with a diagnosis of HGSC, complete medical record data, received 6 series of platinum-based chemotherapy and did not receive neoadjuvant chemotherapy (NAC). Exclusion criteria include archived preparations and paraffin blocks with signs of cell damage due to inadequate fixation, HGSC cases with differential diagnoses and incomplete medical record data. The study sample was a paraffin block of ovarian HGSC patients taken by total sampling. Clinical data including age, FIGO clinical stage, preoperative CA-125 and postchemotherapy CA-125 levels were obtained from the electronic medical record (EMR). Preoperative CA-125 level was measured before debulking surgery. Post-chemotherapy CA-125 levels were measured after receiving 6 series of platinum-based chemotherapy within a maximum of 4 weeks. Data were analyzed as frequency, mean and standard deviation.

CCNE1 Immunohistochemistry

A total of 31 paraffin blocks with diagnosed ovarian HGSC were subjected to CCNE1 (Cyclin E1) immunohistochemistry (rabbit monoclonal antibody clone EP126, 1:200). Paraffin blocks were cut with a thickness of 4 um. Next, deparaffinization, cell conditioning (antigen unmasking) for 60 minutes, with a temperature of 95 degrees, CCNE1 (Cyclin E1) antibody incubation for 30 minutes, UltraView incubation for 10 minutes, incubation with Hematocylin for 16 minutes, and bluing for 4 minutes using a Ventana Benchmark GX IHC system machine. After completion of the process on the device, the slides were removed and washed again in running water. Dehydration in graded alcohol (70%, 96% and 100% alcohol for 5 minutes, clearing in xylol 3 times for 5 minutes, then covered with coverglass. This examination uses positive controls derived from paraffin blocks of clear cell carcinoma ovary for CCNE1 overexpression, placenta for low expression of CCNE1 and germinal center for negative control.

Interpretation was performed by two Anatomic Pathology specialists and researchers using a CX23 microscope at 10 field of view strong magnification (400x) to assess the positivity presentation and intensity of CCNE1 expression. Expression interpretation was grouped into low expression CCNE1 if the tumor cell nucleus was stained ≤ 60% or strongly stained ≤5% of the tumor cell nucleus and overexpression CCNE1 if the tumor cell nucleus was stained >60% and strongly stained > 5% of the tumor cell nucleus.

RESULT

The results (Table 1) showed that of the 31 HGSC patients, more were aged >50 years (61.3%), while patients aged ≤50 years were 38.7%. The mean age of HGSC patients in this study was 51.6 ± 12.1. The majority of patients came at an advanced stage, namely stage III (64.5%) and stage IV (25.8%), the rest were at stage I (9.7%). Most patients (77.4%) had preoperative CA-125 levels ≥500 U/ml. More than half of the patients (58.1%) had CA-125 levels <35 U/ml.

Table 1. distribution clinicopathology characteristics of HGSC patients

Variables	N (31)	%	Mean	Standard deviation
Age			51,6	12,1
≤50 years	12	38,7%		
>50 years	19	61,3%		
Stadium				
Stadium I	3	9,7%		
Stadium II	0	0%		
Stadium III	20	64,5%		
Stadium IV	8	25,8%		
CCNE1 Expression				
Low expression	9	29%		
Overexpression	22	71%		
Preoperative CA-125 levels			3396,7	3933,6
<500 U/ml	7	22,6%		
≥500 U/ml	24	77,4%		
Post-chemotherapy CA-125 levels			51,4	64,8
<35 U/ml	18	58,1%		
≥35 U/ml	13	41,9%		

Of 31 paraffin blocks immunohistochemical examination results showed CCNE1 overexpression in 71% of cases and low expression in 29% of HGSC cases (Figure 1).

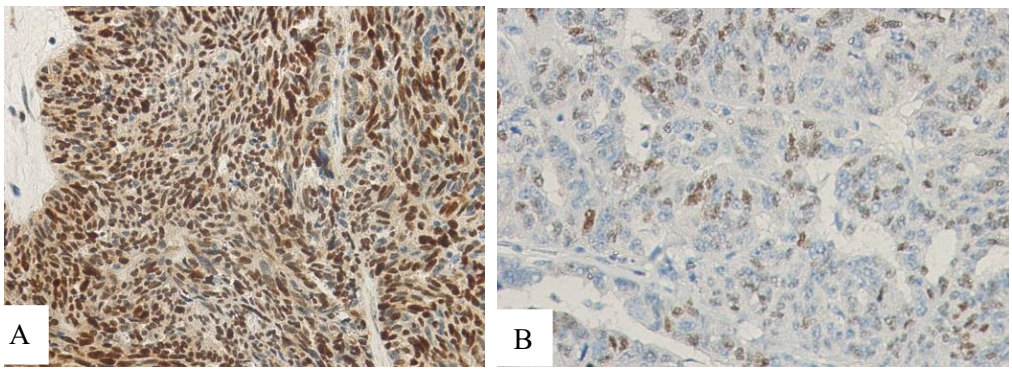

Figure 1 CCNE1 expression. (A) Overexpression of CCNE1. (B) Low expression of CCNE1. (IHC CCNE1, 400X)

DISCUSSION

The result showed that 61.3% of ovarian HGSC patients were over 50 years old, with an average age of 51.6 years. These findings align with research conducted by Tu Mengyan et al who found that the average age of HGSC patients was 54 years.[5] Another study conducted by Chen Ming et al found that the average age of ovarian HGSC patients was 56 years.[16] Aziz Diar et al's research found that the average age was older than this study, which was 60.1 years.[17] This difference is likely that in Azis's research, there were more older HGSC patients than these research, seen from the age range of up to 80 years. Age is one of the risk factors for HGSC. The risk of ovarian HGSC increases

at an older age because it is associated with the accumulation of mutations due to ovulation that occurs continuously and lasts a long time. Ovulation causes the fimbrae part of the fallopian tube to be exposed to the oncogenic content of follicular fluid such as reactive oxygen species (ROS), IGF2 protein, and growth factors such as hepatocyte growth factor (HGF). These oncogenic factors promote carcinogenic changes due to tissue and DNA damage in the epithelium of the fallopian tube fimbrae.[18] The loss of progesterone effect in menopausal conditions also increases the risk of ovarian HGSC. Progesterone plays a role in eliminating tubal epithelial cells damaged by TP53 mutations. [19]

The research showed that most HGSC patients were at advanced stages III (64.5%) and IV (25.8%). These results are in accordance with previous research conducted by Tangdiung et al who found that ovarian HGSC mostly occurred in stages III-IV.[20] Research by Tu Mengyan et al also found that 75% of patients were diagnosed at stages III-IV.[5] This is because most patients only came after there were complaints at an advanced stage so that they were late in receiving treatment. Symptoms and complaints that arise in the early stages are not specific, including abdominal pain, bloating, nausea, constipation, anorexia, diarrhea, and gastric acid reflux.[21] Meanwhile, the most common symptom in the advanced stages is abdominal enlargement with the omentum as the most common metastatic site.[20]

The results of this study found CCNE1 (Cyclin E1) overexpression occurred in 71% of ovarian HGSC patients, higher than previous studies. Nakayama et al found high expression (overexpression) of CCNE1 in 50% of cases, Karst et al in 54%, Ribeiro et al in 46% of cases, Azis et al in 31%, Chan et al in 28.6% and Kang et al in 22.2% of HGSC cases. [4,17,22,23, 24] This difference may be due to differences in scoring methods, cut offs and types of antibodies used. In addition, CCNE1 protein expression is also influenced by the CCNE1 gene transcription process, including a decrease in CCNE1 protein degradation and the presence of retinoblastoma protein deficiency.

The assessment of immunohistochemical examination results in the current study used a cut-off based on the research of Chan et al because they have assessed the sensitivity and specificity tests using CISH examination as a benchmark. ROC analysis on Chan et al's study resulted in ≥60% positivity as the optimal cut-off for predicting CCNE1 amplification (AUC = 0.771). Inter-rater agreement using the ≥60% cut-off reached Cohen's kappa = 0.79 (91.9% inter-rater agreement percentage). Using this cut-off, CCNE1 immunohistochemistry achieved accuracy for predicting CCNE1 amplification (AUC = 0.812) with a sensitivity of 81.6% and specificity of 77.4%. Unsuitable cases were reviewed and it was decided that a positive combination of more than 60% positive tumor cells with at least 5% strongly stained was considered as CCNE1 overexpression. This study used CCNE1 monoclonal antibody clone EP126 which is the same as the study by Chan et al. Positive control of overexpression used clear cell carcinoma ovary, placenta for low expression control and germinal center tonsil for negative control. The results of the Chan et al study found CCNE1 overexpression in 28.6% while in this study as many as 71% of HGSC cases. This difference is likely due to increased transcription of CCNE1 protein which can occur without CCNE1 amplification. This is based on the research of Azis et al who found that almost half of CCNE1 overexpression occurred without CCNE1 amplification.[17]

In addition to CCNE1 gene amplification, increased expression of CCNE1 (Cyclin E1) can occur at various levels of regulation including increased transcription caused by changes in the RB/E2F13 pathway, and decreased protein degradation by FBXW7, an E3 ligase that targets Cyclin E1 for proteolysis.[25] CCNE1 overexpression can occur due to an increase in USP28 protein. The increase in USP28 protein causes a decrease in CCNE1 degradation resulting in an increase in CCNE1

expression[5,26] In addition, the transcription process of CCNE1 is mediated by the transcription factor E2F, which is activated after uncoupling from Rb through a phosphorylation process in late G1 phase. Tumor cells with Rb deficiency cause overexpression of CCNE1 through the transcription factor E2F.[26]

CCNE1 overexpression and CCNE1 amplification are associated with decreased survival in several types of malignant tumors such as bladder cancer, breast cancer and ovarian cancer.[25] In HGSC the prognosis of patients with CCNE1 overexpression is worse than without low expression of CCNE1. The patient's prognosis will get worse if CCNE1 overexpression is accompanied by CCNE1 amplification. Kang et al's found that HGSC patients with CCNE1 overexpression and CCNE1 amplification had a 5-year survival of 28.3%, lower than HGSC patients with low CCNE1 expression and without CCNE1 amplification who had a 5-year survival of 41.9%.[4]

Overexpression of CCNE1 stimulates proliferation in ovarian cancer cells.[22] Overexpression of CCNE1 can induce replication stress, causing disruption of the mitotic process and genomic instability resulting in tumor progression.[27] Karst et al found cyclin CCNE1 expression in precursor, early stage and advanced lesions.[23] This suggests CCNE1 dysregulation is involved in the early stages of tumor progression to metastasis.[28]

CCNE1 amplification or CCNE1 overexpression has emerged as an important biomarker in the HGSC patient population that is resistant to platinum chemotherapy. Ribeiro et al found that ovarian carcinoma patients with CCNE1 overexpression benefited from bevacizumad treatment.[24] Several studies on targeted therapy using WEE kinase inhibitors and CDK2 inhibitors are currently in clinical trials. Another study reported that HGSC with CCNE1 overexpression is highly sensitive to cell cycle checkpoint kinase and immune checkpoint inhibitors combination therapy.[12]

The research found that most patients with HGSC (77.4%) had preoperative CA-125 levels ≥500 U/ml and the remaining 22.6% of patients had preoperative CA-125 levels <500 U/ml. These findings are different from those of Batchman et al. Batchman's study showed that 54.4% of patients had preoperative CA-125 levels ≥500 U/ml and 45.6% had preoperative CA-125 levels <500 U/ml. The difference in the results of the study may be due to the number of samples studied by Batchman et al was more than this study which was 136 ovarian HGSC samples so that it was more varied. This can be seen from the range of preoperative CA-125 levels ≥500 Um/l between 502-48,470 U/ml. Whereas in this study, it is possible that the number of samples studied was smaller and most patients came at an advanced stage with high preoperative CA-125 levels, so that more HGSC patients with preoperative CA-125 levels ≥500 U/ml were obtained.

This study observed a mean preoperative CA-125 level of 3396.7 U/ml which reflected the advanced stage of tumor metastasis. Similar results were reported by Barmon et al who showed a mean preoperative serum CA-125 level of 4537 U/ml with a range between 1745 to 10,987 U/ml.[29] Different results were obtained by Chan et al who obtained a lower mean preoperative CA-125 level of 103 U/ml (range 42-346).[30] Another study by Lee Juhun et al obtained a lower mean postchemotherapy CA-125 level. Lee Juhun et al obtained the mean value of preoperative CA-125 level in the early stage of 299.52±569.18 U/ml, while the preoperative CA-125 level in the advanced stage was 873.42±1391.19 U/ml.[31] This difference was due to Chan's study only examined preoperative CA-125 in the early stage (I, II) while the samples in this study were mostly in the advanced stage III and IV. The mean value of preoperative CA-125 levels in Lee Juhun et al's study was lower than this study probably because Lee Juhun's study not only examined preoperative CA-125 levels in HGSC but also included other ovarian carcinomas. This is in accordance with the research of Lee Maria et al who found that mucinous and endometrioid ovarian carcinoma more

often showed normal CA-125 levels, while elevated CA-125 levels were most often found in serous carcinoma.[32]

Serum CA-125 is a form of secretion of the transmembrane mucin MUC16 secreted by tumor cells and its value is related to the stage and size of the tumor.[33] Vásquez1 et al found an increase in abnormal CA-125 levels (>35 U/mL) occurred in 99% of serous carcinoma with the highest CA-125 value in serous carcinoma compared to other histological subtypes. FIGO III and IV clinical stages showed an increase in CA-125 values compared to stages I and II.[34] The role of CA-125 in tumor development is through the C-terminal domain (CTD) part due to changes in epithelial transition-mesenchymal (EMT). In HGSC progression, the tubal epithelium undergoes changes to undergo partial EMT to form STIC lesions, then spreads to the ovary through the mesenchymal phenotype and finally undergoes mesenchymal-epithelial transition (MET) for tumor formation. Downregulation of E-cadherin with concomitant upregulation of N-cadherin is a key step in EMT. The interaction of CA-125 and mesothelin associated with glycosylphosphatidylinositol initiates cancer cell adhesion to the mesothelium and promotes peritoneal carcinomatosis.[35,36]

The research data showed that 18 HGSC patients (58%) had postchemotherapy CA-125 levels <35 U/ml and 13 HGSC patients (42%) had postchemotherapy CA-125 levels ≥35 U/ml. These findings are in line with the research of Ch Srivalli et al who found that 14 HGSC patients (51.9%) had postchemotherapy CA-125 levels ≤35 U/ml and 13 HGSC patients (48.1%) had postchemotherapy CA-125 levels >35 U/ml. Another study by Barmon et al obtained different results, namely as many as 42% of patients had postchemotherapy CA-125 levels <35 U/ml and 58% of patients had postchemotherapy CA-125 levels >35 U/ml.[29] This difference may be due to Barmon's study only in advanced stages (III, IV) and received neoadjuvant chemotherapy (NACT). Clinical response was obtained if there was no ascites and CA-125 returned to normal values (42% of cases).

This study used a cut-off value of CA-125 level of 35 U/ml based on previous studies. Post-chemotherapy CA-125 levels >35 U/ml were significantly associated with the risk of recurrence.[29,14] Ch Srivalli et al's study concluded that post-chemotherapy CA-125 levels >35 U/ml had a high risk of relapse within 12 months (p value=<0.001). While patients with postchemotherapy CA-125 value <35 U/ml have a risk of recurrence after 12 months which means sensitive to platinum-based chemotherapy. Another study by Lee Maria et al measuring 2-3 weeks after the first, second and sixth cycle after administering platinum-based chemotherapy found that postchemotherapy CA-125 level <35 U/ml after the first cycle was the most important independent prognostic factor in multivariate analysis for overall survival (p value = <0.001) and progression free survival (p value=0.001).[32]

The mean value of CA-125 level after platinum-based chemotherapy in this study was 51.4 ± 64.8 U/ml, which was higher than the research by Lee Maria et al. The results of Lee Maria's study showed that the mean value of postchemotherapy CA-125 levels after the first cycle, second cycle, and sixth cycle of platinum-based chemotherapy were 43.4 (range 6.6-2677.2), 17.1 (range 5.1-3954.5), and 8.8 (range 2.2-9845.5) U/ml, respectively. The difference in these results may be due to the difference in the number of samples, which was 223 people, also due to the presence of residual tumor mass > 1 cm in 45 people (20.2%) of Lee Maria et al.[32] The presence of residual tumor mass was seen from the range of postchemotherapy CA-125 levels which were very high to above 2000 U/ml both after the first, second and sixth cycles. This is consistent with the results of Rema et al that postchemotherapy CA-125 levels >35 U/ml can be associated with residual tumor mass (p value 0.026).[37] In addition, an increase in CA-125 above 35 U/ml also indicates resistance to

chemotherapy and a more aggressive tumor.[36]

One of the mechanisms underlying resistance to platinum chemotherapy is the tumor's surrounding environment that suppresses the immune system.[38] The immune system plays an important role in the antitumor process. Cancer antigen-125 (CA-125) promotes malignant cell replication by inhibiting host immunologic response mechanisms. The CTD MUC 16 portion of CA-125 promotes the increase of Tregs in the tumor environment. Treg cells will facilitate tumor cells to evade the immune response.[36] In addition, this antigen inhibits the destruction of tumor cells by Natural Killer (NK) cells.[39,40]

CONCLUSION

This research showed that HGSC patients were dominated by patients aged >50 years (61.3%), clinical stage FIGO III (64.5%), preoperative CA-125 levels ≥500 U/ml (77.4%) and postchemotherapy CA-125 levels <35 U/ml (58.1%). Measurement of CA-125 levels has prognostic value in HGSC patients. Immunohistochemical examination of CCNE1 showed CCNE1 overexpression in 71% of HGSC. CCNE1 overexpression and CCNE1 amplification are associated with worse patient prognosis. However, CCNE1 overexpression can occur without CCNE1 amplification. For this reason, further molecular examinations such as CISH and FISH are still needed to determine the presence of CCNE1 amplification.

REFERENCES

1. M Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: Epidemiology and risk factors. *Int J Womens Health* 2019;11(7):287-99.
2. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-grade serous ovarian cancer: Basic sciences, clinical and therapeutic standpoints. *Int J Mol Sci* 2019;20(9):1-33.
3. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Pineros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. *Int J Cancer* 2021;149(4):778-89.
4. Kang EY, Weir A, Meagher NS, Farrington K, Nelson GS, Ghatage P, et al. CCNE1 and survival of patients with tubo-ovarian high-grade serous carcinoma: An ovarian tumor tissue analysis consortium study. *Cancer* 2023;129(5):697-713.
5. Tu M, Gao X, Guo T, Lu W, Xu J. Clinicopathological and prognostic factor analyses of primary fallopian tube carcinoma and high-grade serous ovarian cancer. *World J Surg Oncol* 2025;23(1):1-10.
6. Azzalini E, Stanta G, Canzonieri V, Bonin S. Overview of tumor heterogeneity in high-grade serous ovarian cancers. *Int J Mol Sci* 2023; 24(20):1-14.
7. Kanska J, Zakhour M, Taylor-Harding B, Karlan BY, Wiedemeyer WR. Cyclin E as a potential therapeutic target in high grade serous ovarian cancer. *Gynecol Oncol* 2016;143(1):152
8. Talbot T, Lu H, Aboagye EO. Amplified therapeutic targets in high-grade serous ovarian carcinoma – a review of the literature with quantitative appraisal. *Cancer Gene Ther* 2023;30(7):955-63.
9. Hirst J, Crow J, Godwin A. Ovarian Cancer Genetics: Subtypes and Risk Factors. *Ovarian Cancer - From Pathog to Treat*. Published online 2018:3-38. doi:10.5772/intechopen.72705
10. Stronach EA, Paul J, Timms KM, Hughes E, Brown K, Neff C, et al. Biomarker assessment of HR

deficiency, tumor BRCA1/2 mutations, and CCNE1 copy number in ovarian cancer: Associations with clinical outcome following platinum monotherapy. *Mol Cancer Res* 2018;16(7):1103-11.
11. Da Costa AABA, Do Canto LM, Larsen SJ, Ribeiro ARG, Stecca CE, Petersen AH, et al. Genomic profiling in ovarian cancer retreated with platinum based chemotherapy presented homologous recombination deficiency and copy number imbalances of CCNE1 and RB1 genes. *BMC Cancer* 2019;19(1):1-10.
12. Mai J, Yang L, Xie HJ, Li YY, Wang X, Liu XX. Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer (Review). *Oncol Rep* 2022;47(4):1-11.
13. Bachmann R, Brucker S, Stäbler A, et al. Prognostic relevance of high pretreatment ca125 levels in primary serous ovarian cancer. *Mol Clin Oncol* 2020;14(1):1-10.
14. Ch S, V. P. G, G. A. Role of CA 125 in predicting pathological response and recurrence in advanced stage non mucinous epithelial ovarian cancer. *Int J Reprod Contraception, Obstet Gynecol* 2022;11(11):1-6.
15. Chan AMY, Enwere E, McIntyre JB, Wilson H, Nwaroh C, Wiebe N, et al. Combined CCNE1 high-level amplification and overexpression is associated with unfavourable outcome in tubo-ovarian high-grade serous carcinoma. *J Pathol Clin Res* 2020;6(4):252-62.
16. Chen M, Jin Y, Bi Y, Yin J, Wang Y, Pan L. A survival analysis comparing women with ovarian low-grade serous carcinoma to those with high-grade histology. *Onco Targets Ther* 2014;7:1891-9.
17. Aziz D, Etemadmoghadam D, Caldon CE, Au-Yeung G , Deng N, Hutchinson R , et al. 19q12 amplified and non-amplified subsets of high grade serous ovarian cancer with overexpression of cyclin E1 differ in their molecular drivers and clinical outcomes. *Gynecol Oncol* 2018;151(2):327-36.
18. Hsu CF, Seenan V, Wang LY, Chen PC, Ding DC, Chu TY. Human peritoneal fluid exerts ovulation- and nonovulation-sourced oncogenic activities on transforming fallopian tube epithelial cells. *Cancer Cell Int* 2024;24(1):1-12.
19. Wu NYY, Fang C, Huang HS, Wang J, Chu TY. Natural history of ovarian high-grade serous carcinoma from time effects of ovulation inhibition and progesterone clearance of p53-defective lesions. *Mod Pathol* 2020;33(1):29-37.
20. Tangdiung Y, Masadah R, Julian B, Wahid S, Vita G. Clinicopathological Characteristics of high and low-grade Ovarian Serous Carcinoma. *IJSBAR* 2022;62(1):275-80.
21. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynecol Obstet* 2021;155(51):61-85.
22. Nakayama N, Nakayama K, Shamima Y, Ishikawa M, Katagiri A, Iida K et al. Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer. *Cancer*. 2010;116(11):2621-34.
23. Karst AM, Jones PM, Vena N, Ligon AH, Liu JF, Hirsch MS, et al. Cyclin E1 deregulation occurs early in secretory cell transformation to promote formation of fallopian tube-derived high-grade serous ovarian cancers. *Cancer Res* 2014;74(4):1141-52.
24. Ribeiro ARG, Salvadori MM, De Brot L,Bovolin G, Mantoan H, Ilelis F, et al. Retrospective analysis of the role of cyclin E1 overexpression as a predictive marker for the efficacy of bevacizumab in platinum-sensitive recurrent ovarian cancer. *Ecancermedicalscience* 2021;15:1-17.
25. Zhao H, Wang J, Zhang Y, Yuan M, Yang S, Lisong L, et al. Prognostic values of CCNE1 amplification and overexpression in cancer patients: A systematic review and meta-analysis. *J Cancer* 2018;9(13):2397-407.
26. Caldon CE, Musgrove EA. Distinct and redundant functions of cyclin E1 and cyclin E2 in

development and cancer. *Cell Div* 2010;5(9):1-13.
27. Kok YP, Guerrero Llobet S, Schoonen PM, Everts M, Bhattacharya A, Fehrmann RSN, et al. Overexpression of Cyclin E1 or Cdc25A leads to replication stress, mitotic aberrancies, and increased sensitivity to replication checkpoint inhibitors. *Oncogenesis* 2020;9(10):1-15.
28. Margolis B, Dao F, Licciardi M, Misirlioglu S, Olvera N, Ramaswami S, et al. CCNE1 amplification among metastatic sites in patients with gynecologic high-grade serous carcinoma. *Gynecol Oncol Reports* 2021;37:1-5.
29. Barmon D, Patra S, Nandwani M, Jethani R, Kataki AC. Critical Analysis of Advanced High-Grade Serous Epithelial Ovarian Cancer in Women: An Experience of 100 Cases from a Regional Cancer Center in Northeast India. *South Asian J Cancer* 2023;12(4):334-40.
30. Chan JK, Tian C, Kesterson JP, Lin KY, Darcy K, Richardson MT, et al. Gynecologic Oncology Preoperative and pre-chemotherapy CA-125 levels in high-risk early-stage ovarian cancer – An NRG / GOG study. *Gynecol Oncol* 2024;181:54-9.
31. Lee J, Kim JM, Lee YH, Chong GO, Hong DG. Correlation between Clinical Outcomes and Serum CA-125 Levels after Standard Treatment for Epithelial Ovarian Cancer. *Anticancer Res* 2022;42(1):349-53
32. Lee M, Chang MY, Yoo H, Lee KY, Chay DB, Cho H, et al. Clinical significance of CA125 level after the first cycle of chemotherapy on survival of patients with advanced ovarian cancer. *Yonsei Med J* 2016;57(3):580-87.
33. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MA. CA125 and Ovarian Cancer: A Comprehensive Review. Cancers (Basel) 2020;12(12):3730
34. Morales-Vásquez F, Pedernera E, Reynaga-Obregón J, Lopez-Basave HN, Gomora MJ, Carlon E, et al. High levels of pretreatment CA125 are associated to improved survival in high grade serous ovarian carcinoma. *J Ovarian Res* 2016;9(1):1-6.
35. Martin-Hirsch PL, Martin-Hirsch PL, Martin FL. The evolving role of MUC16 (CA125) in the transformation of ovarian cells and the progression of neoplasia. *Carcinogenesis* 2021;42(3):327-43.
36. Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. *Biochim Biophys Acta - Rev Cancer* 2021;1875(2):1-11.
37. Rema P, John ER, Samabasivan S, Prahladan A, George P, Ranjith JS, et al. Evaluation of Computed Tomography Scan and CA 125 Response in Predicting Operability in Advanced Ovarian Cancer and Assessing Survival Outcome in Interval Cytoreductive Surgery. *Indian J Surg Oncol* 2019;10(3):426-34.
38. Mcmullen M, Madariaga A, Lheureux S. New approaches for targeting platinum-resistant ovarian cancer. *Semin Cancer Biol* 2021;77(12):167-81.
39. Muhammad SA, Olaoye SO, Umar FK. Are preoperative serum cancer antigen 125 levels a prognostic factor for outcome in epithelial ovarian cancer ? A systematic review. *Niger Med J* 2024;65(2):108-18.
40. Fraser CC, Jia B, Hu G, Johani LIA, Fritz-Klaus R, Ham JD, et al. Ovarian Cancer Ascites Inhibits Transcriptional Activation of NK Cells Partly through CA125. *J Immunol* 2022;208(9):2227-38.