Is there any difference in insulin resistance status between cases of benign and malignant ovarian neoplasms? A study on surrogate markers of insulin resistance in Indonesian non-diabetic women

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Abstract. The association between insulin resistance (IR) and ovarian neoplasm is little known. The present study attempted to investigate the difference in clinicopathological characteristics, metabolic parameters, and IR prevalence between benign and malignant ovarian neoplasms. The cross-sectional study involved 52 non-diabetic women with benign (n=27) and malignant (n=25) diagnoses in a tertiary hospital in Indonesia. Fasting insulin level (FIL), homeostatic model assessment of IR and β-cell dysfunction (HOMA-IR and HOMA-β), fasting IR index (FIRI), and quantitative insulin sensitivity check index (QUICKI) were used as surrogate markers to evaluate IR. Parametric and nonparametric statistical tests were employed to analyze the different parameters between the two groups. Pearson or Spearman's rank test assessed the correlation between markers and clinical variables. Results revealed that patients with benign neoplasms were younger than those with malignant neoplasms (38.63 vs. 47.40 years; P=0.003) and had a higher median body mass index (BMI) than their counterparts (22.98 vs. 18.61 kg/m^2; P=0.014). Different characteristics between benign and malignant neoplasm cases were found in menopausal status, ovary side affected, systolic blood pressure, and BMI classes. Endometrial cysts and mucinous carcinoma were the most often diagnosed benign and malignant neoplasms. Malignant neoplasms had a lower median HOMA-β score than benign neoplasms (49.33 vs. 75.79; P=0.011), indicating more severe β-cell dysfunction. No significant difference was observed in the prevalence of IR between benign and malignant ovarian neoplasms for the following values of each marker: FIL (25.9% vs. 12.0%), HOMA-IR (37.0% vs. 28.0%), FIRI (51.9% vs. 48.0%) and QUICKI (81.5% vs. 92.0%). The indicators of FIL, HOMA-IR, HOMA-β, FIRI, and QUICKI correlated with each other and confirmed the reliability of these surrogate markers for measuring IR status in ovarian neoplasms. In brief, benign ovarian neoplasms tended to have more IR when compared with malignant ovarian neoplasms. However, this difference was not statistically significant.

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Abbreviations: BC, breast cancer; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; FIL, fasting insulin level; FIRI, fasting insulin resistance index; FPG, fasting plasma glucose; HEC, hyperinsulinaemic-euglycaemic clamp; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; IGF, insulin-like growth factor; IGFBP, insulin growth factors binding proteins; IOTA, International Ovarian Tumor Analysis; IR, insulin resistance; QUICKI, quantitative insulin sensitivity check index; RLU, relative light unit; SBP, systolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SHS, senior high school; T2DM, type 2 diabetes mellitus; US, ultrasound; WHO, World Health Organization

Key words: HOMA-IR, HOMA-β, fasting insulin level, insulin resistance, FIRI, QUICKI, benign ovarian neoplasm, malignant ovarian neoplasm, surrogate markers, Indonesia

Introduction

Ovarian neoplasm accounts for 6.6% of all female neoplasms (1) and has emerged as one of the most prevalent types of gynecological cancer in Western nations and is also an emerging type of cancer in Asia (2). Ovarian neoplasm survival in Indonesians is poor (3), with its mortality rate surpassing that of cervical and endometrial cancer (4). Ovarian neoplasm is the third most common cancer in women in Indonesia, with incidence rates of 10 per 100,000 individuals, 14,896 new cases in 2020, and a mortality rate of 4.1% (5). According to a recent study, 80% of all ovarian neoplasms are benign (6). Others are malignant, with epithelial ovarian carcinoma (EOC) accounting for 90% of ovarian cancers (7).

The effects of the Western lifestyle have been linked to chronic high blood glucose, obesity, and insulin resistance (IR), all of which are included in metabolic syndrome (MetS) (8). Through insulin-like growth factor (IGF) signaling, IR induces hyperinsulinemia and has a mitogenic and anti-apoptotic effect (9,10). These contribute to the development of multisite cancer (11), especially in individuals who consume more food with a higher glycemic index (12). Hyperinsulinemia has been linked to an increased risk of ovarian cancer in women after menopause (13), and thus it would be another obstacle that would significantly influence cancer outcomes. Several investigations have studied the link between IR and cancer in general (14) and cancer in women, namely cancer of the breast (15-21), endometrium (16,22) and cervix (16). However, despite obesity being a well-known risk factor for ovarian cancer (23), limited evidence supports the role of IR in ovarian neoplasm (16,24,25), and controversies arise regarding whether IR prevalence is different between benign and malignant neoplasms (24-26).

In a previous study of non-diabetic post-menopausal Chinese women with ovarian neoplasms, researchers discovered that the prevalence of ovarian neoplasms was twice as high in the insulin-resistant group as it was in the insulin-sensitive group (16). However, no prior research in Indonesia has studied the difference in IR prevalence between benign and malignant ovarian neoplasms, and no current research has studied surrogate indicators of IR in these two types of ovarian neoplasms. The present study aimed to examine the clinicopathological characteristics, metabolic indicators, and prevalence of benign and malignant ovarian neoplasms in Indonesian women. Fasting insulin level (FIL), homeostatic model assessment of IR (HOMA-IR), homeostasis model assessment of β-cell dysfunction (HOMA-β), fasting IR index (FIRI), and quantitative insulin sensitivity check index (QUICKI) were some of the novels, robust surrogate markers the present study attempted to evaluate in correlation with IR status. The present study also intended to investigate the correlations between the markers and the relationships between the markers and clinical characteristics. Based on IR status and body mass index, it sought to establish a connection between clinicopathological and metabolic variables and ovarian neoplasm grouping by IR status and body mass index (BMI).

Materials and methods

Research design, study population, and inclusion and exclusion criteria. The present study was an analytical cross-sectional study investigating surrogate markers of IR in benign and malignant ovarian neoplasms patients in Dr. Cipto Mangunkusumo Hospital, a referral hospital for cancer in Indonesia, between October 2019 and 2020. The minimum required sample was calculated using a statistical formula for a comparative test of numerical data of two unpaired groups that were carried out in one measurement (27,28) as stated below:

$$n_1 = n_2 = 2\left(\frac{[Z_\alpha + Z_\beta]^2 \pi}{X_1 - X_2}\right)^2$$

In this formula, 'n_1 and n_2' denoted the number of subjects in each group (benign and malignant). 'Z_α' was the standard value of α obtained from the z-curve, with a value of 1.96, and '$Z\beta$' is the standard value of type two error (β=0.8), with a value of 0.84. The notation of 'π' is the sum of two standard deviations (SDs) of HOMA-IR, as a common marker of IR, in the malignant group (SD=0.5) and benign group (SD=0.6) of ovarian neoplasm and thus π value was 1.1 (24). The mean score difference of the HOMA-IR deemed significant between the two groups was indicated by 'X_1-X_2', with 2.8 being the value judged by the researchers to be significantly different (a prior study determined it as 0.5, but the result was not statistically significant) (24).

Following calculation, the present study obtained a minimum number of subjects per group of 18.97 (~19). However, it adopted a consecutive nonrandom sampling method and enlisted 80 subjects with ovarian cysts suspected as neoplasms who were admitted to inpatient or outpatient services in the ward. Fig. 1 describes the selection of subjects based on inclusion and exclusion criteria. After all eligible patients had given informed consent, transvaginal, transabdominal, or transrectal ultrasound (US) was performed by an experienced examiner to initially classify the neoplasms as benign or malignant while waiting for histopathological confirmation. The initial grouping followed the assessment of different neoplasias in the adnexa risk model developed by the International Ovarian Tumor Analysis (IOTA) (29,30). Clinical characteristics and blood sampling were obtained preoperatively, and histopathological examination results confirmed the final grouping after the surgical procedure (resection or biopsy).

Data extraction, measurement of parameters, and definition of variables. Data were extracted from the identity cards of patients, history, and medical records. Sociodemographic variables included the hometown, age, education, and occupation of patients. The province where the patient resided within the last year was recorded based on the identity card and domicile letter (31). The rurality variable was created by categorizing the patients' domicile into rural, suburban, and urban areas based on the Indonesian Statistics Agency data (32-34). The age was classified into ranges per decade and categorized into young (≤40 years) and old age (>40 years) based on productivity and reproductive age (35,36) and relevant studies (37,38). Formal education was categorized based on their level of educational status to be low level [primary and junior high school (JHS)] or high-level education [senior high school (SHS) and bachelor's degree)] (39). Employment status was categorized as employed or unemployed (39).

The present study analyzed parity status, contraception use, menopausal status and age, specimen type, affected ovarium site (left/right), cancer stage, and histopathological examination results through medical records, surgical reports, and pathological reports. A prior study classified parity status into nulliparous, primiparous, and multiparous (3). Contraception status was classified by different methods of contraception that the subjects had ever used, such as hormonal or non-hormonal contraception, pill or non-pill, and injection or non-injection (3). Menopausal status was defined as a cessation of the menstrual cycle for 12 months and was classified based on a prior study (3). Specimen types were divided into biopsy or resection specimens. The history of cancer pointed to the presence of any malignancies in the close/nuclear family. The affected side of the ovary included the left, right,

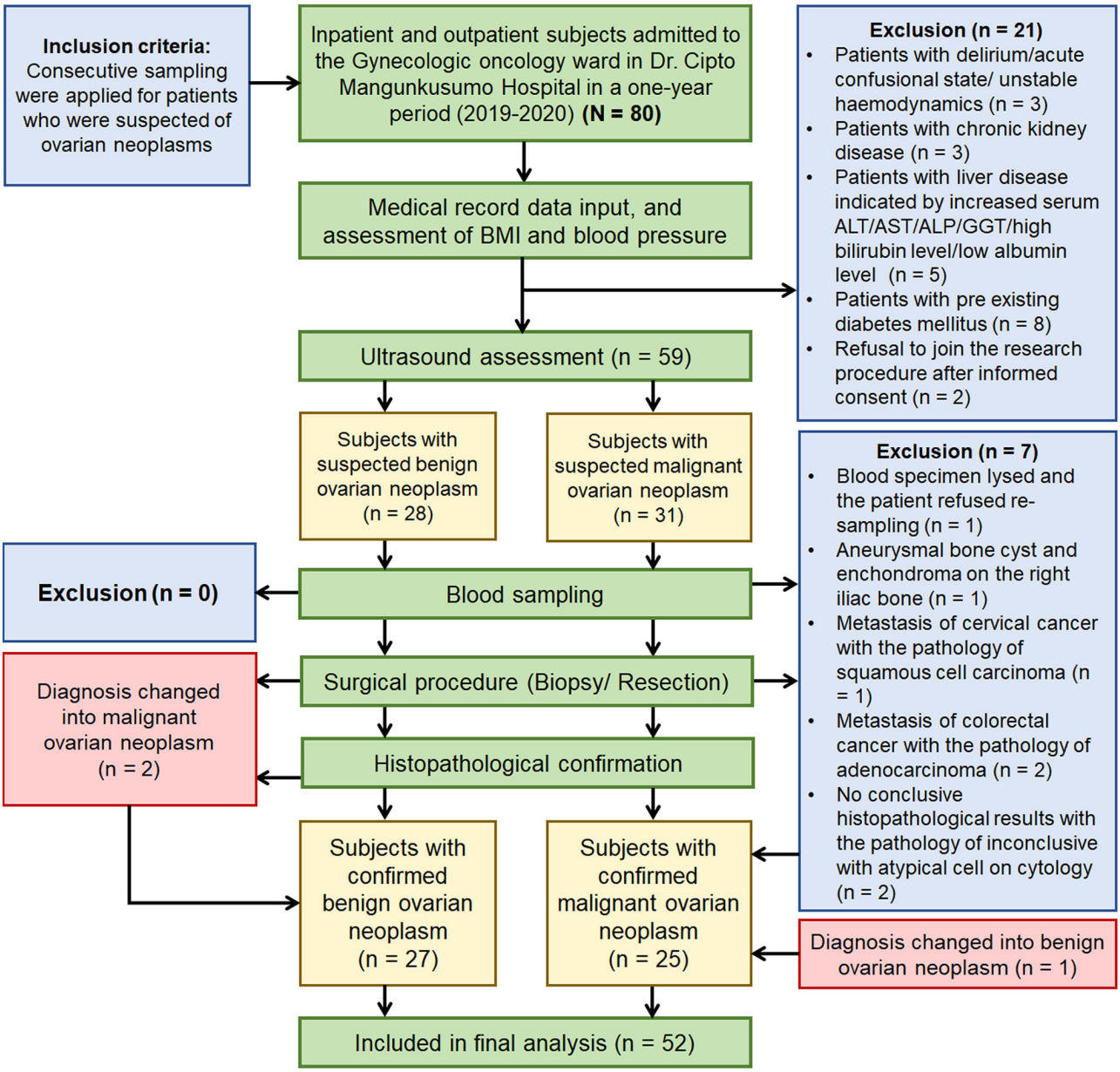

Figure 1. Flow diagram of subjects designated in the research analysis. Participants were selected following inclusion and exclusion criteria before inputting medical record data and ultrasound assessment. Some patients were excluded from the cohort after blood sampling and histopathological confirmation. Changes in the diagnosis from benign to malignant neoplasms and vice versa adjusted the number of cases in these two groups of ovarian neoplasm for the final analysis. ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; and BMI, body mass index.

or bilateral ovary depending on the location of the neoplasm found at diagnosis. The cancer stage was grouped as early (I-II) and advanced stage (III-IV) cancer, as classified by The International Federation of Gynecology and Obstetrics (40). Experienced gynecological-oncologist consultants performed the determination of the cancer stage. Histopathological examination results were obtained from post-surgical samples and confirmed benign or malignant pathological diagnoses and other concurrent pathological findings based on World Health Organization (WHO) criteria (41). The malignant neoplasms can histologically be classified as an epithelial, germ cell, sex cord-stromal, other specific non-epithelial, and non-specific histological types (42).

The present study measured blood pressure (BP) and documented prior hypertension history, BMI, fasting plasma glucose (FPG), and FIL in metabolic parameters. The systolic and diastolic blood pressure (SBP and DBP) were doubly measured using a clinically validated digital sphygmomanometer (Omron HEM-7120; OMRON Healthcare Asia) with a standard protocol of measurement of BP (43). The results of SBP and DBP were classified based on the 2020 Global Hypertension Practice Guidelines (43). BMI was computed using height and weight data from calibrated hospital scales following adult anthropometrics standard procedures (44). The Asia Pacific standard's specific threshold was applied to classify BMI (45), which was then divided into two groups (normal + underweight and overweight + obese).

All blood sampling and recording of clinical data were performed before surgery. A venous blood sample was taken to measure FPG and FIL in the morning after overnight fasting.

Following universal standard precautions, 6 ml of peripheral venous blood was collected from the antecubital vein by venipuncture into red and grey sterile Vacutainer tubes from participants who had fasted overnight (8-12 h) (46). Blood in the grey tube was used for FPG analysis using a hexokinase enzymatic reference method (47). Meanwhile, blood in the red tube was chilled immediately and allowed to clot within 30-45 min. Then, the clotted blood was centrifuged at 1,300-2,000 x g for 15 min at 4˚C. After obtaining the serum (supernatant), it and the aliquot were put into two sample cups, each with a volume of 0.5 ml. The remaining aliquots were stored at -80˚C until assayed. The procedures used in this investigation were based on a previous study (48).

Insulin was quantified using the chemiluminescence technique with a standardized ADVIA Centaur ReadyPack assay (Bayer AG). The ADVIA insulin examination is a two-site sandwich immunoassay using direct chemiluminescence technology, employing two antibody types. The first antibody, in Lite Reagent, is a labeled mouse insulin monoclonal antibody conjugated to acridinium ester. The second antibody, a solid-phase mouse insulin monoclonal antibody, was attached to a paramagnetic particle. These two antibodies react with the insulin in the sample and produce a luminescent emission captured by the photomultiplier and translated into a Relative Light Unit (RLU). This RLU value is proportional to the insulin concentration in the sample. This process was referred to in a study by Gupta *et al* (49).

The present study employed three FPG criteria as given in the guidelines by the American Diabetes Association in 2022 (50). Criteria for high FIL were defined from receiver operating characteristic (ROC) curve analyses in a previous study with a cut-off of <7 μIU/ml to exclude IR (51). The present study employed several surrogate markers [i.e., HOMA-IR (52,53), HOMA-β (52-55), FIRI (56-58), and QUICKI (59-62)] with the following equations to quantify IR prevalence:

$$\text{HOMA} - \text{IR} = \text{fasting insulin level } \left(\frac{\mu\text{IU}}{\text{ml}}\right) \times \frac{\text{fasting plasma glucose } \left(\frac{\text{mg}}{\text{dL}}\right)}{405}$$

$$\text{HOMA} - \beta = 360 \times \frac{\text{fasting insulin level } \left(\frac{\mu\text{IU}}{\text{ml}}\right)}{\text{fasting plasma glucose } \left(\frac{\text{mg}}{\text{dL}}\right) - 63} \%$$

$$\text{FIRI} = \frac{\text{fasting insulin level } \left(\frac{\text{mg}}{\text{dL}}\right)}{18} \times \frac{\text{fasting insulin level } \left(\frac{\mu\text{IU}}{\text{ml}}\right)}{25}$$

$$\text{QUICKI} = \frac{1}{[\log \text{fasting insulin level } (\mu\text{IU/ml})] + [\log \text{fasting plasma glucose } (\text{mg/dL})]}$$

HOMA-IR was used to evaluate IR and calculated with a HOMA calculator released in MDCalc (mdcalc.com/homa-ir-homeostatic-model-assessment-insulin-resistance). The present study used a cut-off of HOMA-IR specific for Indonesian women with IR and MetS with a value of ≥1.208 noted as IR and 'normal' if the result is <1.208 (63).

HOMA-β classification depicts the function of the pancreatic β-cells (64). The classification used for the HOMA-β tests was determined by an Asian study from Japan using a cut-off point by tertile: ≤76.25 (low value; suggesting β-cell dysfunction); 76.25-122.13 (medium value; indicating normal β-cell function); and ≥122.13 (high; suggesting the excessive function of insulin secretion in β-cells, commonly found in central obesity) (53).

Duncan *et al* (57) formulated FIRI derived from FIL and FPG, which has been validated as an empirical IR index against the hyperinsulinaemic-euglycaemic clamp (HEC) (65). The original formula for FIRI in a previous study used FPG in mmol/l (66), hence the present study modified it to be adjusted in mg/dl by dividing the FPG by 18 [FPG (mmol/l)=FPG (mg/dl)/18] (67). A lower result of FIRI reflected a normal-level value, and the cut-off >0.77 denoted IR based on the AUC value in a prior study (68).

The QUICKI is the inverse of the HOMA-IR and assesses insulin sensitivity instead of IR (69) and a value <0.339 indicated IR (59-62).

Ethical clearance. An Institutional Ethical Reviewer Board from the Faculty of Medicine Universitas Indonesia authorized this research, with the ethical clearance number KET-1091/UN2.F1/ETIK/PPM.00.02/2019. The eligible subjects gave full written consent to this research regarding the present study's purpose and procedure. This study followed the Strengthening the reporting of observational studies in epidemiology checklist guidelines for cross-sectional studies (70).

Statistical analysis. All collected data were analyzed using the Statistical Package for the Social Sciences software (v24; IBM Corp.) and visualized using Microsoft Excel for Microsoft 365 MSO (v2205; 32-bit edition; Microsoft Corporation). After completing a Levene's test for homogeneity of variances following the normality test using the Kolmogorov-Smirnov or Shapiro-Wilk tests, normally distributed continuous data were expressed as a mean score and standard error or as median score [interquartile ranges (IQR)] if they were skewed in distribution. Employing an independent Student's t-test or its alternate statistical test (the Mann-Whitney U test), numerical data of clinical and metabolic parameters were compared between cases of benign and malignant neoplasms, whereas for categorical data, χ^2 or Fisher exact tests were used.

P<0.05 indicated a statistically significant difference with a 95% confidence interval (CI). Pearson's correlation analysis or Spearman's rank test was used depending on data variance. Their correlation value (r) or rho degree (ρ) was interpreted according to the standard: 0, no correlation; 0.01-0.2, very weak correlation; 0.2-0.4, weak correlation; 0.4-0.6, moderate correlation; 0.6-0.8, strong correlation; 0.8-1, very strong correlation; and 1, monotonic correlation (71).

Results

Sociodemographic, clinicopathological and metabolic profiles. In the present study, 52 subjects were selected, consisting of 27 (51.92%) with benign neoplasm and 25 (48.08%) with malignant neoplasm. The majority of the patients came from urban areas (67.3%), then suburban areas (19.2%), and then rural areas (13.5%). Five different provinces were identified, with residents of Jakarta representing the majority of participants (53.9%), followed by those from West Java (26.9%), Banten (15.4%), Bangka Belitung (1.9%), and Yogyakarta (1.9%). Unemployed subjects made up 61.5% of the population. More than 60% of women had a high level of formal education, including a bachelor's degree (19.2%) and SHS (42.3%). Meanwhile, almost 40% of women possessed a low level of formal education comprised of primary school

Table I. Comparison of patient's sociodemographic and clinical characteristics between the two ovarian neoplasm classifications.

	Ovarian neoplasms						
	Benign		Malignant		Total		
Characteristics	n	%	n	%	n	%	P-value
Age (years)							0.123[a]
11-20	1	3.7	0	0	1	1.9	
21-30	8	29.7	1	4.0	9	17.3	
31-40	7	25.9	6	24.0	13	25.0	
41-50	6	22.2	8	32.0	14	26.9	
51-60	4	14.8	9	36.0	13	25.0	
61-70	1	3.7	1	4.0	2	3.9	
Age category (years)							0.023[a]
Young (≤40)	16	59.3	7	28.0	23	44.2	
Old (>40)	11	40.7	18	72.0	29	55.8	
Marital status							>0.999[b]
Married	23	85.2	22	88.0	45	86.5	
Unmarried	4	14.8	3	12.0	7	13.5	
Parity status							0.449[a]
Nulliparous	9	33.3	8	32.0	17	32.7	
Primiparous	3	11.1	6	24.0	9	17.3	
Multiparous	15	55.6	11	44.0	26	50.0	
Menopausal status							0.026[a]
Yes	6	22.2	13	52.0	19	36.5	
No	21	77.8	12	48.0	33	63.5	
Fertility drug use							>0.999[b]
Yes	1	3.7	1	4.0	2	3.8	
No	26	96.3	24	96.0	50	96.2	
Malignancy history in the family							>0.999[b]
Yes	1	3.7	1	4.0	2	3.8	
No	26	96.3	24	96.0	50	96.2	
Contraception use							0.242[a]
No	21	77.8	16	64.0	37	71.2	
Pill	2	7.4	1	4.0	3	5.8	
DMPA	0	0	4	16.0	4	7.7	
DMPA, pill	3	11.1	1	4.0	4	7.7	
DMPA, IUD	0	0.0	1	4.0	1	1.9	
IUD	1	3.7	1	4.0	2	3.8	
IUD, pill	0	0	1	4.0	1	1.9	
Contraception type							0.262[a]
None + non-hormonal	22	81.5	17	68.0	39	75.0	
Hormonal	5	18.5	8	32.0	13	25.0	
Oral contraception use							0.705[b]
No	22	81.5	22	88.0	44	84.6	
Yes	5	18.5	3	12.0	8	15.4	
Injection contraception use							0.284[b]
No	24	88.9	19	76.0	43	82.7	
Yes	3	11.1	6	24.0	9	17.3	
Specimens from diagnostic procedures							0.002[a]
Biopsy	9	33.3	0	0	9	17.3	
Resection	18	66.7	25	100.0	43	82.7	

Table I. Continued.

Characteristics	Ovarian neoplasms						P-value
	Benign		Malignant		Total		
	n	%	n	%	n	%	
Ovarium side affected							0.036[b]
Left	5	18.5	8	32.0	13	25.0	
Right	6	22.2	11	44.0	17	32.7	
Bilateral	16	59.3	6	24.0	22	42.3	
SBP (mmHg)							0.043[a]
Normal (<130)	17	63.0	11	44.0	28	53.8	
High-normal (130-139)	8	29.6	4	16.0	12	23.1	
Grade I (140-159)	2	7.4	8	32.0	10	19.2	
Grade II (≥160)	0	0	2	8.0	2	3.9	
DBP (mmHg)							0.377[a]
Normal (<85)	18	66.7	13	52.0	31	59.6	
High-normal (85-89)	7	25.9	6	24.0	13	25.0	
Grade I (90-99)	2	7.4	5	20.0	7	13.5	
Grade II (≥100)	0	0	1	4.0	1	1.9	
Prior hypertension history							0.053[a]
No	20	74.1	12	48.0	32	61.5	
Yes	7	25.9	13	52.0	20	38.5	
BMI Asia-Pacific classification (kg/m^2)							0.061[a]
Underweight (<18.5)	4	14.9	11	44.0	15	28.9	
Normal (18.5-22.9)	10	37.0	9	36.0	19	36.5	
Overweight (23-24.9)	8	29.6	2	8.0	10	19.2	
Obese (≥25)	5	18.5	3	12.0	8	15.4	
BMI class							0.033[a]
Lower-class BMI (normal + underweight)	14	51.9	20	80.0	34	65.4	
Higher-class BMI (overweight + obese)	13	48.1	5	20.0	18	34.6	

[a]χ^2 test; [b]Fisher exact test. SHS, senior high school; DMPA, depot-medroxyprogesterone acetate; IUD, intrauterine device; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

(21.2%) and JHS (17.3%). Subjects had a mean age of 42.9±11.0 (range 17-65 years). As shown in Table I, the proportion between young and old patients was comparable (55.8% vs. 44.2%), corresponding with the significantly different mean score between patients with benign and malignant neoplasms (38.63±11.43 vs. 47.40±8.63, P=0.003) in Table II. The majority of the participants were married, had multiple children, were not menopausal, did not use contraception, had no family history of cancer, had both ovaries affected by tumors, had normal levels of SBP and DBP, did not previously have hypertension, and were within the normal weight range according to BMI.

The differences in sociodemographic and clinical characteristics between benign and malignant ovarian neoplasms cases were found in the variable of age category (P=0.023), menopausal status (P=0.026), specimen taking (P=0.002), affected side of ovary (P=0.036), SBP (P=0.043), and BMI class (P=0.033). Table II shows that the patients with malignant neoplasms had a lower mean score of BMI than those with benign tumors [18.61 (IQR: 17.97-21.32) vs. 22.98 (20.08-24.44), P=0.014]. It also demonstrates that malignant cases had a lower median HOMA-β score than their counterparts [49.33 (IQR: 28.06-84.44) vs. 75.79 (IQR: 59.29-102.86), P=0.011].

As illustrated in Table III, the most frequent diagnosis in cases of benign neoplasms was an endometrial cyst (59.3%), followed by mucinous cystadenoma (25.9%) and mature teratoma (18.5%). Mucinous carcinoma (40% of all malignant neoplasm cases), clear cell carcinoma (24%), and adenocarcinoma (16%) were the three most prevalent malignant neoplasm types. Among the malignant cases, 5 patients (20%) had stages I-II, and 20 patients (80%) had stages II-IV of the disease.

Prevalence of IR in ovarian neoplasms. The prevalence estimation of IR among Indonesian patients with ovarian neoplasms ranged from 19.2% using FIL to 86.5% using QUICKI, depending on the selected surrogate marker (Table IV). According to these results, β-cell dysfunction affected 61.5% of patients concurrently. For any application of the markers, there was no statistically significant difference

Table II. Differences in mean or median values of clinical characteristics of patients and metabolic parameters between the two ovarian neoplasm classifications.

Variables	Mean ± SD or median (IQR)			P-value[a]
	Benign ovarian neoplasms	Malignant ovarian neoplasms	All cases	
Age (years)	38.63±11.43	47.40±8.63	42.85±11.01	0.003[b]
Menopausal age (years)	48.50±4.37	48.08±4.37	48.21±4.25	0.847[b]
SBP (mmHg)	121.70±13.14	129.40±17.88	125.40±15.92	0.081[b]
DBP (mmHg)	80.00 (78.00-85.00)	84.00 (79.00-89.50)	82.00 (78.00-87.75)	0.078[c]
BMI (kg/m^2)	22.98 (20.08-24.44)	18.61 (17.97-21.32)	20.39 (18.36-24.19)	0.014[c]
FPG (mg/dl)	82.00 (79.00-96.00)	94.00 (78.00-100)	84.00 (79.25-96.00)	0.241[c]
FIL (μIU/ml)	3.20 (4.20-7.70)	3.60 (2.75-5.15)	4.00 (2.95-5.87)	0.105[c]
HOMA-IR	0.82 (0.57-1.73)	0.79 (0.54-1.29)	0.82 (0.58-1.50)	0.318[c]
HOMA-β (%)	75.79 (59.29-102.86)	49.33 (28.06-84.44)	65.14 (42.91-99.07)	0.011[c]
FIRI	0.81 (0.54-1.56)	0.74 (0.54-1.16)	0.76 (0.54-1.35)	0.327[c]
QUICKI	0.39 (0.35-0.42)	0.40 (0.37-0.42)	0.39 (0.36-0.42)	0.307[c]

[a]P-value indicated the statistical differences between benign and malignant neoplasms group; [b]Student's t-test, equal variances assumed; [c]Mann-Whitney U test. SD, standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIL, fasting insulin level; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; FIRI, fasting insulin resistance index; QUICKI, quantitative insulin sensitivity check index.

in the prevalence of IR and β-cell dysfunction between benign and malignant cases. However, subjects with benign neoplasms tended to have IR more commonly (FIRI, 51.9% vs. 48%; HOMA-IR, 37% vs. 28%; and FIL, 25.9% vs. 12%). On the other hand, malignant neoplasms tended to have more significant β-cell dysfunction according to HOMA-β (72% vs. 51.9%) and more frequent IR according to QUICKI (92% vs. 81.5%). All cases with high FPG ≥126 mg/dl (n=2) also belonged to malignant neoplasms cases.

Correlation between clinical features and surrogate markers. Three different correlation analyses were performed among markers, and between markers and clinical features, done in the overall subject pool, and the benign and malignant ovarian neoplasm groups, respectively. As shown in Fig. 2A, there was a strong positive correlation between FIL and FIRI, HOMA-IR and FIRI, age and menopausal age, and FIL and HOMA-IR among all ovarian neoplasm cases. There was also a strong negative correlation between QUICKI and FIRI, QUICKI and FIL, and QUICKI and HOMA-IR. Fig. 2B shows that among the 'benign group,' there was a strong positive correlation between FIL and FIRI, HOMA-IR and FIRI, and FIL and HOMA-IR. A strong negative correlation was also discovered between QUICKI and FIRI, QUICKI and FIL, and QUICKI and HOMA-IR. Fig. 2C expresses a significant positive correlation among the malignant group between FIRI and FIL and between FIRI and HOMA-IR; meanwhile, a strong negative correlation was identified between QUICKI and FIRI, QUICKI and FIL, and QUICKI and HOMA-IR.

Association between patients' characteristics and ovarian neoplasms according to IR and BMI. Table V shows that the difference between the two groups of IR status (non-IR vs. IR) was observed among the benign neoplasm group in the median score of FIL (P<0.001) and HOMA-β (P=0.031), as well as in the mean scores of FPG (P=0.004), FIRI (P<0.001), and QUICKI (P<0.001). Meanwhile, among the malignant neoplasms group, the mean score of FPG (P=0.002) and the median score of FIL (P=0.001), FIRI (P<0.001), and QUICKI (P<0.001) were significantly different between the IR and non-IR groups. More detailed analysis in Table SI (in categorical data) revealed that among benign neoplasms cases, parity status (P=0.039), FPG (P=0.041), FIL (P<0.001), FIRI (P<0.001), and QUICKI (P=0.012) differed between the two groups of IR status. Meanwhile, the parameters of FPG (P=0.036), FIL (P=0.015), and FIRI (P=0.002) were shown to differ between the non-IR and IR groups among malignant neoplasm cases.

The difference between 'higher-class' and 'lower-class' BMI status among benign and malignant patients was examined in Table VI. Among patients with benign neoplasms, it was discovered that the median score of FPG (P=0.017) and HOMA-β (P=0.023) was significantly different between the two groups of BMI status (overweight + obese vs. normal + underweight). Meanwhile, among patients with malignant diagnoses, there was no significant variation in mean/median score parameters between the two groups of BMI status. Further categorical data analysis, as the details attached in Table SII, revealed a significant difference in DBP (P=0.009), hypertension status (P=0.039), and HOMA-β (P=0.041) variables between the two BMI statuses within the malignant neoplasms group.

Association between characteristics of patients and histopathological types of ovarian cancer. There was no significant variation in patient characteristics regarding clinical, metabolic,

Table III. Description of histopathological diagnosis in the benign and malignant ovarian neoplasm cases.

	Total	
Histopathological diagnosis	n	%
Primary ovarian neoplasm diagnosis		
Benign pathology	27	51.9
Malignant pathology	25	48.1
Presented benign histopathological diagnosis[a]		
Endometrial cyst	16	59.3
Mucinous cystadenoma	7	25.9
Mature teratoma	5	18.5
Dermoid cyst	3	11.1
Ovarian abscess	3	11.1
Chronic xanthogranuloma oophoritis	2	7.4
Brenner tumor	1	3.7
Seromucinous cystadenoma	1	3.7
Cellular fibroma	1	3.7
Presented malignant histopathological diagnosis		
Mucinous carcinoma	10	40.0
Clear cell carcinoma	6	24.0
Adenocarcinoma	4	16.0
Endometrioid carcinoma	2	8.0
Serous carcinoma	2	8.0
Mixed type (mucinous carcinoma and clear cell carcinoma)	1	4.0

[a]Since some patients may display more than one benign neoplasm diagnosis in the pathological examination; thus, multiple responses were recorded and analyzed.

and IR indicators among histopathological types of malignant ovarian neoplasm, as shown in Table VII and Table SIII. However, patients with serous carcinoma seemed to have the oldest age, the oldest age at which menopause occurs, the greatest BMI score, the highest FIL, the highest HOMA-IR, and the greatest FIRI. Meanwhile, the mixed histopathological type group had the highest SBP, DBP, and FPG levels and the lowest BMI and HOMA-β score. These two subtypes also shared the lowest QUICKI results.

Discussion

Limited evidence is available on the association of IR with ovarian neoplasm (16,24,49), particularly among Southeast Asians. Thus the present study investigated whether there is a difference in IR between benign and malignant ovarian neoplasm since IR plays a vital role in FIL homeostasis related to cancer.

Characteristics of patients with benign and malignant ovarian neoplasms. Not surprisingly, due to the massive urbanization and adoption of a sedentary lifestyle associated with Western society in Indonesia, the patients in the present study predominantly came from urban areas with high education levels. This lifestyle may lead to a rising incidence of obesity-related comorbidities, including ovarian neoplasms, as observed in urban areas of China compared with rural areas (2,72,73). Nevertheless, living in an urban area with a high education does not guarantee that patients will be diagnosed early since cases in the present study were predominantly in advanced-stage diseases (80%). Indeed, ~75% of cases of ovarian cancer are diagnosed at a late stage due to the non-specific nature of symptoms and the absence of practical screening tests (49).

The present study revealed that most of the patients were old (>40 years), similar to a study conducted in India (49), with young women mostly having benign ovarian neoplasm (Table I). Meanwhile, older women were more commonly involved in malignant cases. Different ages were also found to exhibit different histological subtypes; serous subtypes were more common in older patients and adenocarcinoma in younger patients. Generally, a younger age pattern was found among all histological subtypes compared with a study by Otokozawa *et al* (25). The present study found no significant difference in other clinical risk factors of ovarian cancer, such as menopausal status, parity, and contraceptive use, between malignant and benign neoplasm patients, similar to a prior study in India (49).

There were no differences in the clinicopathological characteristics of patients with ovarian neoplasm according to IR status, BMI status, cancer stage, and histological subtypes among the benign and malignant case groups. However, the present study found a higher proportion of patients with high SBP (grade I and II) in malignant compared with benign neoplasms (40% vs. 7.4%; $P<0.05$). Hypertension is

Table IV. Comparison of metabolic parameters related to the prevalence of insulin resistance between the two ovarian neoplasm classifications.

	Ovarian neoplasms						
	Benign		Malignant		Total		
Parameters	n=	%	n=	%	n=	%	P-value
FPG (mg/dl)							0.193[a]
Normal (<100)	24	88.9	18	72.0	42	80.8	
Moderate (100-125)	3	11.1	5	20.0	8	15.4	
High (≥126)	0	0	2	8.0	2	3.8	
FIL (μIU/ml)							0.296[b]
Normal (<7)	20	74.1	22	88.0	42	80.8	
IR (≥7)	7	25.9	3	12.0	10	19.2	
HOMA-IR							0.488[a]
Normal (<1.208)	17	63.0	18	72.0	35	67.3	
IR (≥1.208)	10	37.0	7	28.0	17	32.7	
HOMA-β (%)							0.300[a]
Normal β-cell function (76.25-122.13)	8	29.6	5	20.0	13	25.0	
Beta cell dysfunction (≤76.25)	14	51.9	18	72.0	32	61.5	
Beta cell excessive function (≥122.13)	5	18.5	2	8.0	7	13.5	
FIRI							0.781[a]
Normal (≤0.77)	13	48.1	13	52.0	26	50.0	
IR (>0.77)	14	51.9	12	48.0	26	50.0	
QUICKI							0.352[b]
Normal (>0.339)	5	18.5	2	8.0	7	13.5	
IR (≤0.339)	22	81.5	23	92.0	45	86.5	

[a]χ^2 test; [b]Fisher exact test. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIL, fasting insulin level; IR, insulin resistance; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; FIRI, fasting insulin resistance index; QUICKI, quantitative insulin sensitivity check index.

an age-related disease, and those with malignant ovarian neoplasm are more commonly elderly. Hypertension may occur in these patients due to psychological states or pain, involving a maladaptive nociceptive system (74). IR, which is associated with activation of the renin-angiotensin-aldosterone system and sympathetic nervous system activities, could also contribute to the patients' high blood pressure in this study (75).

The most intriguing finding of the present study was that those with benign ovarian neoplasms were more likely to be overweight or obese compared with those with malignant neoplasms. In this study, the predominance of patients with a lower BMI status in malignant neoplasms was probably related to protein-energy wasting caused by chronic leptin dysregulation due to persistent systemic inflammation (76). This process leads to reduced appetite and intake, weight loss, malnutrition, and possibly cachexia (77). The results were comparable to a study in South Korea that found that underweight and normal BMI prevalence in advanced-stage ovarian cancer was 44% (vs. 3.3%) and 36% (vs. 45%), respectively (78). Wright *et al* (79) also confirmed that women having 'normal' BMI categories (35.2%) are more likely to suffer malignant ovarian neoplasm compared with overweight (23.9%) or obese (25.8%) women. Nevertheless, according to a study in the US, BMI demonstrated a poor positive association with ovarian cancer (OR 1.14, 95% CI: 0.86-1.51) (80).

Measuring IR in benign and malignant ovarian neoplasms. In Indonesia, there is no established investigation on surrogate markers for IR in ovarian neoplasms, and there is no universally accepted definition of IR based on these various markers. The present study enrolled non-diabetic women with benign and malignant neoplasms to measure their IR status using numerous surrogate markers proposed in the literature (56). Accordingly, the prevalence of IR in the Indonesian patients in the present study ranged from 19.2-86.5% in overall cases depending on different markers used, 25.9-81.5% in the benign case group, and 12-92% in the malignant case group, varying based on the diagnostic markers and selected cut-offs used. These numbers were comparable with the prevalence of IR in benign cases (28.7%) and malignant cases of breast neoplasm (64.0%) in Turkey (15), as well as the prevalence of IR in endometrial carcinoma (80%) in China (22). IR prevalence is attributed to different populations, inclusion criteria, markers, and cut-offs to define IR. In the investigation of IR,

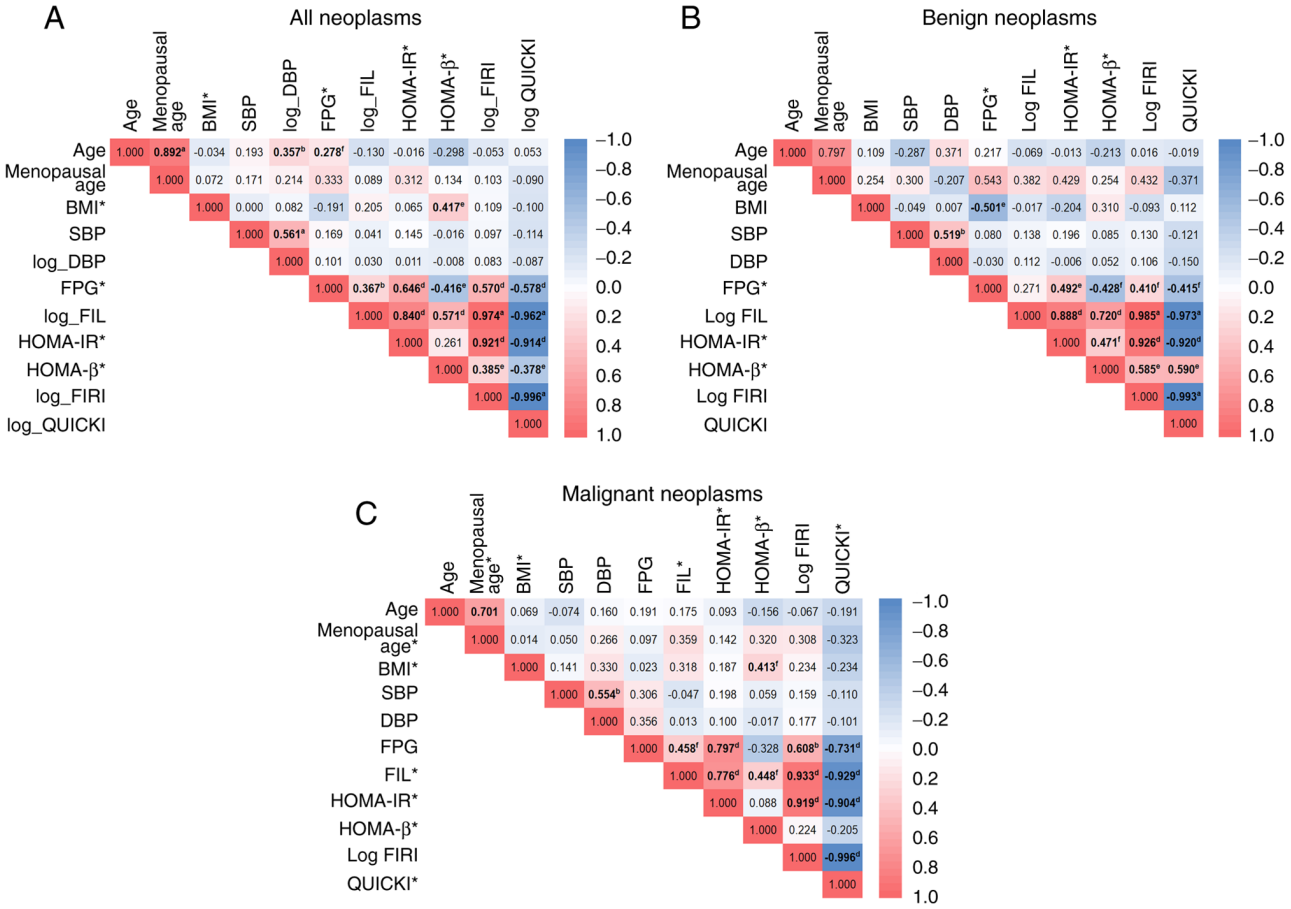

Figure 2. Correlation plot between clinical features and surrogate markers of insulin resistance among the entire, benign, and malignant case groups. (A) Among all ovarian neoplasm cases, the highest positive correlation was revealed between FIL and FIRI (r=0.974), and the strongest negative correlation was found between FIRI and QUICKI (ρ=-0.996). (B) Considering benign cases, FIL possesses the most potent positive correlation with FIRI (r=0.985), and FIRI was most negatively correlated with QUICKI (r=-0.993). (C) In the sub-analysis for malignant cases, FIL and FIRI had the most robust positive correlation (ρ=0.933); meanwhile, FIRI and QUICKI possessed the firmest correlation value with ρ=-0.996. [a]P<0.001 from Pearson's correlation test; [b]P<0.01 from Pearson's correlation test; [c]P<0.05 from Pearson's correlation test; [d]P<0.001 from Spearman's rank correlation test; [e]P<0.01 from Spearman's rank correlation test; [f]P<0.05 from Spearman's rank correlation test. *Skewed data distribution in the normality test using the Kolmogorov-Smirnov test for overall patients and the Shapiro-Wilk test for respectively the benign and malignant case groups, although adjustments for normalization have been made. Thus, the usual correlation test was Spearman's statistical test; other variables without asterisks were tested using the Pearson correlation test. Logarithmic variables resulted from transformed variables to allow them to be normalized in distribution. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIL, fasting insulin level; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; FIRI, fasting insulin resistance index; QUICKI, quantitative insulin sensitivity check index.

the result revealed no difference in prevalence statistically between benign and malignant ovarian neoplasms. This was in agreement with Serin *et al* (24), who reported that the IR index by HOMA is not a valid indicator for ovarian malignancy. A study by Lukanova *et al* (26) also reported no significant association of IR-related circulating blood marker [i.e., insulin growth factors binding proteins-3 (IGFBP-3)] with ovarian cancer risk. Hernandez *et al* (81) also reported no differences in IR markers, including FIL, in women with breast cancer (BC), while Kundaktepe *et al* (82) showed no differences in FPG and HOMA-IR between BC cases and healthy controls.

In contrast with the findings of the present study, Sun *et al* (16) found that the prevalence of post-menopausal malignant neoplasm of the ovary was higher in patients with IR (0.17 vs. 0.09%; P<0.05) with OR of 2.17 (95% CI: 1.22-3.89; P<0.05) than those who were insulin sensitive (16). Research in India discovered that a high level of FIL in ovarian neoplasm is associated with a greater risk for cancer development with an OR of 2.7 (95% CI: 1.00-6.67; P<0.05) (49). Otokozawa *et al* (25) also documented an increased risk of malignant ovarian neoplasm in the high tertile of FIL compared with the low tertile (P trend <0.001).

The lack of significance between the benign and malignant groups in the present study's findings may be due to the different proportions of subject BMIs, with higher rates of obese and overweight patients in the benign group. Meanwhile, the malignant group's BMI was more typically normal or underweight. Variations in study characteristics might be another cause for these discrepancies. Several factors influence serum IGF-I concentrations in individuals with IR, including age, nutritional intake, and underlying disease severity (83). A study discovered a tangible link between circulating IGF-I levels and the risk of getting ovarian cancer before age 55 (26); meanwhile, most of our patients had a younger age with a mean age of 42.9 years. The most recent studies studied IR and ovarian neoplasm in individuals who were primarily menopausal (16,24,49), which was not the case in the present study.

Table V. Differences in mean or median values of clinical characteristics of patients and metabolic parameters between non-insulin-resistant and insulin-resistant groups among benign and malignant ovarian neoplasms.

	Mean ± SD or median (IQR)					
	Benign neoplasms			Malignant neoplasms		
Variables	Non-IR (HOMA-IR <1.208)	IR (HOMA-IR ≥1.208)	P-value	Non-IR (HOMA-IR <1.208)	IR (HOMA-IR ≥1.208)	P-value
Age (years)	39.18±10.64	37.70±13.22	0.753[a]	46.11±7.88	50.71±10.19	0.239[a]
Menopausal age (years)	46.50 (43.00-50.75)	52.00 (50.00-52.00)	0.165[b]	48.00±1.85	48.20±7.15	0.940[a]
SBP (mmHg)	121.18±12.32	122.60±15.07	0.792[a]	130.50±16.96	126.57±21.23	0.632[a]
DBP (mmHg)	81.06±5.85	80.50±6.75	0.227[a]	83.83±6.51	86.14±7.99	0.462[a]
BMI (kg/m^2)	23.13±3.11	21.14±3.61	0.145[a]	18.66 (17.89-20.88)	18.61 (18.36-24.97)	0.671[b]
FPG (mg/dl)	82.06±6.05	92.00±10.59	0.004[a]	85.50±15.55	109.71±15.77	0.002[a]
FIL (μIU/ml)	3.60 (2.80-4.10)	7.95 (6.87-13.30)	<0.001[b]	3.15 (2.45-3.87)	5.60 (4.90-7.90)	0.001[b]
HOMA-β (%)	65.25 (49.20-101.83)	86.72 (64.84-249.04)	0.031[b]	47.53 (28.02-81.48)	65.03 (28.00-91.74)	0.672[b]
FIRI	0.66±0.19	1.91±0.57	<0.001[a]	0.62 (0.43-0.82)	1.37 (1.17-1.65)	<0.001[b]
QUICKI	0.41±0.20	0.34±0.14	<0.001[a]	0.41 (0.39-0.44)	0.36 (0.35-0.37)	<0.001[b]

[a]Student's t-test, equal variances assumed; [b]Mann-Whitney U test. SD, standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIL, fasting insulin level; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; FIRI, fasting insulin resistance index; QUICKI, quantitative insulin sensitivity check index.

Table VI. Differences in mean or median values of patient's clinical characteristics and metabolic parameters between the two classes of body mass index among benign and malignant ovarian neoplasms.

	Mean ± SD or median (IQR)					
	Benign ovarian neoplasms			Malignant ovarian neoplasms		
Variables	Normal + underweight	Obese + overweight	P-value	Normal + underweight	Obese + overweight	P-value
Age (years)	39.29±12.60	37.92±10.50	0.764[a]	47.25±8.58	48.00±9.82	0.866[a]
Menopausal age (years)	49.00 (43.00-53.50)	48.50 (47.00-48.50)	>0.999[b]	49.00 (46.00-50.00)	49.50 (49.00-49.50)	0.611[b]
SBP (mmHg)	123.00±14.02	120.31±12.53	0.604[a]	126.45±16.52	141.20±20.12	0.100[a]
DBP (mmHg)	80.50±7.23	81.23±4.80	0.762[a]	83.30±6.97	89.20±4.15	0.085[a]
FPG (mg/dl)	86.50 (81.75-96.25)	80.00 (76.50-83.50)	0.017[b]	91.65±20.24	94.80±13.53	0.746[a]
FIL (μIU/ml)	4.80 (2.76-7.12)	4.00 (3.45-8.45)	0.560[b]	3.65±1.68	7.40±5.29	0.190[c]
HOMA-β (%)	62.23 (49.80-85.91)	102.86 (70.52-161.84)	0.023[b]	43.16 (27.77-73.44)	77.14 (57.40-110.45)	0.067[b]
FIRI	0.96 (0.51-1.58)	0.74 (0.61-1.77)	0.865[b]	0.69 (0.46-1.13)	0.98 (0.79-2.87)	0.089[b]
QUICKI	0.39±0.04	0.38±0.04	0.895[a]	0.40 (0.37-0.43)	0.38 (0.33-0.39)	0.097[b]

[a]Student's t-test, equal variances assumed; [b]Mann-Whitney U test; [c]Student's t-test, equal variances not assumed. SD, standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIL, fasting insulin level; IR, insulin resistance; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; FIRI, fasting insulin resistance index; QUICKI, quantitative insulin sensitivity check index.

Menopause, which involves hormonal changes, might affect IR by contributing to increased visceral adiposity, which is linked to IR in post-menopausal women (17). This hypothesis might answer why the present study could not get significant differences between the benign and malignant case groups, mainly because of the generally younger age of patients involved in this study and fewer patients in our study group having menopausal status. Additionally, the prevalence of IR

Table VII. Differences in mean or median values of patient's clinical characteristics and metabolic parameters among the different histopathological types of malignant ovarian neoplasm.

	Median (IQR)						
Variables	Mucinous carcinoma	Clear cell carcinoma	Adenocarcinoma	Endometrioid carcinoma[b]	Serous carcinoma[b]	Mixed type[b]	P-value[c]
Age (years)	45.50 (40.00-53.25)	46.00 (40.25-50.50)	38.00 (31.50-52.00)	52.50	62.00	56.00	0.085
Menopausal age (years)	48.50 (45.75-49.75)	46.50[a]	43.00[a]	49.50	52.50	50.00	0.300
SBP (mmHg)	138.00 (116.75-152.75)	121.00 (106.00-140.25)	116.50 (115.00-130.75)	130.00	130.00	140.00	0.553
DBP (mmHg)	82.50 (77.25-90.75)	85.50 (80.00-90.50)	80.50 (77.00-87.00)	85.00	85.50	90.00	0.680
BMI (kg/m^2)	20.04 (17.89-24.84)	18.66 (17.98-25.44)	18.49 (17.24-18.93)	19.84	21.66	18.36	0.904
FPG (mg/dl)	87.50 (80.50-102.50)	87.50 (70.25-115.25)	83.50 (72.25-98.50)	92.50	96.00	126.00	0.651
FIL (μIU/ml)	3.50 (2.85-4.55)	3.00 (1.83-6.82)	5.30 (3.20-7.40)	3.10	6.55	4.90	0.245
HOMA-IR	0.73 (0.58-1.14)	0.73 (0.26-1.79)	0.82 (0.15-1.66)	0.70	1.56	1.52	0.433
HOMA-β (%)	49.30 (36.53-78.92)	26.13 (-20.15-87.48)	94.47 (57.23-201.30)	38.73	71.08	28.00	0.260
FIRI	0.66 (0.52-1.02)	0.66 (0.23-1.61)	0.99 (0.56-1.50)	0.63	1.40	1.37	0.293
QUICKI	0.40 (0.38-0.42)	0.40 (0.37-0.52)	0.37 (0.35-0.42)	0.41	0.36	0.36	0.308

[a]IQR could not be determined since few menopause patients with clear cell carcinoma (n=2) and adenocarcinoma (n=2); [b]IQR could not be determined since few cases of endometrioid carcinoma (n=2), serous carcinoma (n=2) and mixed type of malignant ovarian neoplasm (n=1); [c]P-value indicated the statistical differences between the six pathology types of malignant ovarian neoplasm using the Kruskal-Wallis test. IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIL, fasting insulin level; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; FIRI, fasting insulin resistance index; QUICKI, quantitative insulin sensitivity check index.

is also closely related to obesity (84); by contrast, the present study had fewer obese and overweight participants, and in malignant cases, the subjects mainly had lower BMI; thus, the IR difference will also probably be statistically insignificant between the two groups.

Recent research into ovarian cancer has revealed that different histopathological types may have different risk factors, unique carcinogenesis, and distinct developmental pathways (85,86). Accordingly, the present study conducted a comparative histopathological analysis of malignant ovarian neoplasms related to clinical, metabolic, and IR indicators. The results, however, revealed no significant variation for these comparisons. Nonetheless, based on FIL, HOMA-IR, and FIRI markers, it was discovered that IR tended to be more prevalent in serous carcinoma groups. There has been a limited exploration into the various histopathological types of ovarian cancer and IR. The present study, however, corroborated previous findings in a case-control study, which reported that the proportion of MetS is more prominent in the serous carcinoma group compared with the other histopathological groups (69.44% vs. 30.56%, P=0.411) (87). The highest median BMI score in the ovarian cancer patients in the present study was also found in the serous carcinoma group. This result supported evidence from a previous Mendelian randomization study, which indicated that genetically predicted increasing BMI (per 5 kg/m^2) was linked with an increased risk of low-grade serous ovarian cancers (87). Notably, a higher triacylglycerol level is associated with a greater risk of serous ovarian cancers (88). However, the sample size of each histopathological type of ovarian cancer in this provided data was small, making it challenging to draw convincing conclusions concerning these qualities. More research, therefore, is demanded to validate these findings.

Study on surrogate markers of IR between benign and malignant ovarian neoplasms. The measurement of IR should be seen as heralding the possibility of future changes in the understanding of ovarian neoplasm development. The HEC

is a standard and direct approach for estimating IR currently. However, because of the time and cost needed (89), its application in clinical practice is restricted. As a result, there is a need for accessible and approachable tests to evaluate insulin sensitivity/resistance (56). Several studies have focused on more practical ways of assessing IR using calculated markers (52,61,90).

As the main component of IR markers, FPG is crucial in determining the probability of reactive glucose and type 2 diabetes mellitus (T2DM) development. In the current investigation, the variations in IR markers and FPG parameters between the benign and malignant case groups were not statistically significant. However, there was a tendency for a slightly greater proportion of women with *de novo* high FPG in malignant cases rather than in benign cases. This insignificant difference might be related to the lower BMI status and metabolic parameters of the patients in the present study compared with those in other studies. Chronic hyperglycemia in patients with cancer may develop due to IR, which reduces glucose uptake in the muscle tissue and glucose storage in the liver, leading to elevated blood glucose levels (15).

Measuring the FIL and FPG is the most convenient and accurate method for determining IR in the normoglycemic population (91,92). The concentration of FIL was strongly correlated with the estimated insulin action (r=0.61; P<0.001) (93). However, it did not address the inappropriately low insulin secretion in the face of hyperglycemia, as found in diabetic or glucose-intolerant patients (56). Although a study with a cut-off of ≥7 μIU/ml indicated that the sensitivity of FIL was reasonably high (92.19%) with poor specificity (59.04%) for excluding IR (51), the present study discovered that FIL with the same cut-off could not distinguish the IR status difference in our case groups.

The HOMA model has proved to be a robust clinical and epidemiological tool for assessing IR (HOMA-IR) and β-cell function (HOMA-β). HOMA-IR correlates well with the HEC tests (94), with a sensitivity of 86%, specificity of 100%, and accuracy of 88% (66). No difference was found between benign and malignant cases using the Indonesian cut-off (63). HOMA-β is another computed variable demonstrating basal insulin secretion of pancreatic β-cells (95), indicating either normal, reduced, or excessive function. Insulin levels depend on the pancreatic β-cell effect on glucose concentrations. Thus, the diminished response of β-cell to secrete insulin with glucose stimulation will echo the impaired function of the β-cells of the subjects (62,96,97).

Similarly, IR is reflected in the diminished suppressive effect of insulin on hepatic glucose production (56). The present study found a statistically significant lower median score of HOMA-β in the malignant neoplasm group compared with the benign neoplasm group (49.33 vs. 75.79; P=0.011), and both of their median scores were classified as β-cell dysfunction (Table II). In the early phases of IR development, pancreatic β-cells release excessive insulin, resulting in hyperinsulinemia. Blood glucose levels will rise as β-cells become exhausted, depleted, and dysfunctional, eventually developing T2DM (98). This research has therapeutic implications, indicating that combining anti-tumor and anti-hyperglycemic medications may result in better tumor reduction outcomes (99). The present study observed the different mean scores of HOMA-β between the IR and non-IR groups and between two classes of BMI classes among benign neoplasm cases; meanwhile, there was no statistical difference among malignant cases. It was probably due to the lower prevalence of obese and overweight participants in the malignant group, thus making the marker measurement results less reliable (64).

Another derived IR marker is FIRI, with a sensitivity of 86%, specificity of 100%, and accuracy of 88% (66). Among all patients with ovarian neoplasms, the present study revealed that the median score of FIRI was 0.76 (IQR: 0.54-1.35) and was not significantly different between the benign and malignant groups. FIRI is the most robust positively correlated parameter with FIL in the overall subjects, benign, and malignant case groups. It can indicate a cluster of pathologies, including hypercholesterolemia, T2DM, hypertension, and cardiovascular disease, indicating that they share a common etiology in IR (100). FIRI and HOMA reflect hepatic insulin sensitivity (90).

The last marker, QUICKI, has been found to have greater accuracy, stronger correlation (r=0.78), and improved positive predictive power to HEC compared with HOMA-IR (r=0.6) (56,61,101) in estimating insulin sensitivity (61,102). This marker has a sensitivity of 84%, specificity of 100%, and accuracy of 86% (66). The present study identified 86.5% of IR cases using this marker, similar to a prior study with a percentage of 84.4% (66). The median score of QUICKI in the present study was 0.39 (IQR: 0.36-0.42), with no significant difference between the two case groups, presumably because this index is lower in non-diabetic subjects than in patients with MetS, T2DM, and obesity (56). QUICKI is simply the logarithm of HOMA-IR, which explains the near-perfect correlation with HOMA, as seen in Fig. 2. Given the similarities between QUICKI and HOMA, these two approaches compare well (56) and have a strong correlation with FIL (P<0.01) (103). Nevertheless, according to the literature, HOMA-IR and QUICKI are limited due to their inability to provide information on the activity of insulin receptors in assessing IR (104).

Correlation between clinical features and surrogate markers. The correlation between markers and between markers and clinical variables related to insulin sensitivity (i.e., QUICKI) and IR (FIL, HOMA-IR, HOMA-β, FIRI) as reported by prior studies (66,104) are presented in Fig. 2. The strongest positive correlations were observed between FIL and FIRI among all neoplasm cases (r=0.974), benign (r=0.985) and malignant cases (ρ=0.933). FIL was correlated with HOMA-IR and HOMA-β in all three groups at decreasing strengths, respectively. Another study also found a positive correlation between FIL and HOMA-IR (r=0.93) and between FIL and FIRI (r=0.93) (66). Rutter *et al* (105) also report a correlation between FIL and HOMA-IR. Focusing on their link with clinical data, the present study found that HOMA-β was moderately correlated with BMI in the overall case group (ρ=0.417).

Similarly, the strongest significant inversely correlations were found between QUICKI and FIRI among the overall (r=-0.996), benign (r=-0.993), and malignant (ρ=-0.996) case groups. At a lesser strength, QUICKI was inversely correlated with FIL, HOMA-IR, FPG, and HOMA-β among the overall

case group, with FIL, HOMA-IR, HOMA-β, and FPG among the benign group and with FIL, HOMA-IR, and FPG among the malignant group. A similar result between QUICKI and FIL (r=-0.92) was also found in a previous study (66). Evaluating their correlation with clinical data, the current investigation discovered an inverse correlation between HOMA-β and FPG among overall cases and the benign case group, as well as between QUICKI and FPG in all three groups. These results were not entirely different from findings in a study on melanoma, which highlights the importance of HOMA-IR and QUICKI, which correlate between each marker and clinical data (104). Similarly, Conwell *et al* (106) reported that HOMA-IR, QUICKI, and FIL strongly correlate with IR. Overall, these findings confirm the reliability of the surrogate marker tests to determine IR status and their correlation with essential clinical data, as well as their interchangeability in assessing IR.

Compared to QUICKI and HOMA measurements, the FIL test exhibited excellent levels of sensitivity and specificity (107). In a previous study, Gates *et al* (100) discovered that FIRI substantially correlated with MetS-related characteristics. Meanwhile, Rudvik and Månsson (108) propose HOMA-IR, QUICKI, and FIRI as the best approach for estimating IR in clinical practice, attributed to their high correlation with HEC.

The mechanism between IR and malignant ovarian neoplasm is explained by the stimulation of IGF-1, a peptide hormone generated by excessive insulin. Anti-apoptotic and mitogenic properties of IGF-1 will promote tumor formation in ovarian epithelial cells (26,77,109). Karasik *et al* (110) confirm that IGF-1 concentrations are higher in cystic fluid from malignant ovarian neoplasms than in cystic fluid from benign ovarian neoplasms. IGF-1 is also released by hepatocytes and adipocytes, which explains why this peptide is linked to obesity (111,112). High insulin levels can promote peripheral estrogen transformation by affecting the expression of adipose tissue aromatase P450c17 in the ovarian glands (22,113). Together with insulin, estrogen will trigger the proliferation of the stroma, granulose cells, and theca cells (114,115).

Ovarian cancer is metabolically active and boosts its capacity to uptake larger volumes of glucose by upregulating the expression of glucose transporters (116-118). Chronic hyperglycemia creates DNA damage, cellular dysfunction, and damage to the ovarian epithelium by exposure to produced oxidative stress (i.e., reactive oxygen species) and the effects of glycation (119,120). In hyperglycemic environments, the interaction of advanced glycation end products and their receptors has been demonstrated to enhance tumor cell proliferation or invasiveness (121) by promoting systemic inflammation. High concentrations of cytokines (IL-1, TNF-α, IL-6, IL-8, and TGF-β) and prostaglandin, which promote mutagenesis and impede cellular recognition and destruction of tumors, are hypothesized to be connected with cancer development mechanistically (8,122). Higher glucose levels also contribute to increased angiogenesis in tumors by upregulating the expression of pro-angiogenic factors (e.g., VEGF) (123).

The critical finding of this study was that by applying multiple simple and specific cut-off surrogate markers, we could identify IR in more than two-thirds of this Indonesian case group with ovarian neoplasms. Considering the role of insulin in ovarian carcinogenesis, the results suggested that individuals with benign ovarian neoplasms and a higher BMI status, particularly those with metabolic comorbidities, should be cautiously investigated for IR. A greater BMI should be a concern since it may alter circulating hormone levels and growth factors, leading to enhanced carcinogenesis and the possibility of malignant transformation (124).

Strengths and limitations. The present study was the first in Indonesia, to the best of the authors' knowledge, to report clinicopathological factors associated with IR in newly diagnosed Asian patients with ovarian neoplasm. It will be helpful for further scientific development and policy-makers due to a paucity of evidence in this area. Patients with T2DM and chronic inflammatory illnesses were also excluded from the study to avoid bias and false-positive high insulin levels.

However, although the outcomes of the present study are clinically worthwhile, several drawbacks might arise. First, this research was performed in a single center. Second, this cross-sectional study also does not prove causality; thus, it is challenging from a healthy population standpoint to infer if the diseases begin from IR to ovarian neoplasm or vice versa (8). The third limitation is that the sample size was relatively small; thus, type II errors may have occurred in the study. Nevertheless, earlier research on this issue also used a small sample size with similar settings (24,25,49,59) and the sample size of the present study was more extensive than those. Fourth, the present study did not recruit a healthy control group, making it impossible to assess and compare the development of the neoplasm case group to a normal state. The present study also did not use the standard technique to confirm IR (i.e., HEC) for this study (125); however, WHO has suggested surrogate markers to be diagnostic tools for IR in epidemiological research (126). Sixth, the cut-offs adopted in this study were not entirely based on the Indonesian women population with ovarian neoplasm because no initial investigation had established those cut-offs for Indonesians. Finally, the pre-menopausal and post-menopausal groups for each case group (benign and malignant) were not studied because their proportions were unequal.

In conclusion, there was no significant difference in IR between benign and malignant ovarian neoplasms among Indonesian non-diabetic women, as measured by numerous surrogate markers of IR. However, benign ovarian neoplasms tended to have a slightly higher proportion of IR. A tendency for a slightly higher proportion of IR was also found in advanced-stage cancer and serous carcinoma. QUICKI is likely superior in showing the highest prevalence of IR among the three groups. The present study also discovered considerable β-cell dysfunction in both case groups, with a more severe occurrence in malignant neoplasms, indicating early MetS and possible correlations to IR. Since insulin affects multiple pathways signaling cancer development, monitoring FIL, FPG, and other IR surrogates might be practical and integrative approaches to therapeutic cancer targets. To better understand the effect of IR on ovarian carcinogenesis and progression, a multicenter and population-based study with long-term follow-up on women with ovarian neoplasms should be conducted. It is also necessary to adjust BMI, age, menopausal status, comorbidities, and histopathological diagnosis to precisely stratify susceptibility to IR. Future research should measure other IR surrogate markers, including the glucose/insulin ratio, insulinogenic

index, Matsuda index, Gutt index, Stumvoll index, Avignon index, oral glucose insulin sensitivity index, sex hormones, leptin and other inflammatory markers (56). Investigations should also focus on more specific markers like IGF-I and IGFBP-3, which might be more accurate in distinguishing between benign and malignant ovarian neoplasms.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HW was the principal investigator of this study, acquired funding, and controlled the decision to publish. HW, MH and ISF confirm the authenticity of all the raw data and accepted full responsibility for the overall content of the work. HW, MH, and ISF conceptualized the study, performed the investigation, designed the methodology, and provided the resources. HW and MH contributed to the analysis and drafted the manuscript. MH and ISF collected the data and performed the project administration. MH was entirely responsible for software utilization, data cleaning, and visualization of research findings. HW, FK, KHN, TDA, TWU and ADP performed the cancer staging, supervised the study and validated all data analyses. All authors critically revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Faculty of Medicine, Universitas Indonesia, with the ethical clearance number KET-1091/UN2. F1/ETIK/PPM.00.02/2019 and protocol number 19-07-0831. Written informed consent has been obtained from all patients involved in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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