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Original Article

Immunonutrition in ovarian cancer: clinical and immunological impact?

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ABSTRACT

Objective: Malnutrition is frequent in ovarian cancer (OC) patients and may compromise post-operative outcomes. The aim of this study is to evaluate the impact of pre-operative immunonutrition on the surgical outcome of OC patients, and on their nutritional, inflammatory and peripheral blood immune status.
Methods: A prospective study was performed between September 2016 and April 2020. Immune-enhancing enteral nutrition was administered to 42 patients before surgery according to their nutritional status assessed by the Malnutritional Universal Screening Tool. Biochemical and hematological monitoring was performed before and after immunonutrition. Post-operative outcomes were assessed and compared with those of a similar group of patients treated without nutritional support.
Results: Of the 42 immune-nourished patients, 23 (54.8%) had a low, 11 (26.2%) an intermediate and 8 (19%) a high risk of malnutrition. After the immunonutritional intake, significant variations of prealbumin, creatinine and white blood cells were detected. All T cell populations had an increasing trend, in particular $CD3^+$ T lymphocytes (p=0.020), $CD3^+CD8^+$ cytotoxic T lymphocytes (p=0.046) and lymphocyte with HLA-DR expression (p=0.012). The rate of grade II–III post-operative complications was lower (21.4% vs. 42.9%, p=0.035) and the time of hospitalization was shorter (7.5 vs. 9.2, p=0.009) in the immune-nourished group.
Conclusion: Pre-operative immunonutrition improves the surgical outcome of OC patients. After immunonutrition, an increase of $CD3^+CD8^+$ cytotoxic T lymphocytes was observed.

Keywords: Ovarian Cancer; Immunonutrition; Immune Response; Perioperative Management; Surgical Outcomes

Synopsis

Immune-modulating formulas could stimulate patients' immune response and modulate control of inflammatory response. Pre-operative immunonutrition could reduce the length of hospitalization and postoperative complications. The increase of T lymphocytes, in particular $CD3^+CD8^+$ cytotoxic ones, may enhance the anti-tumor immune response.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Malnutrition is frequent in cancer patients and can be induced by the tumor or by cancer treatments. It may be driven by inadequate food intake, decreased physical activity and metabolic derangements, host- or tumor-derived, leading to catabolic alterations with a systemic inflammatory syndrome, that impacts on metabolic pathways [1]. Malnutrition could compromise the body reaction to external stress factors, like major abdominal surgery.

Surgery, especially major abdominal surgery, cause an inflammatory, immune and oxidative stress. An unbalanced inflammatory response after surgery may vary from a hyperinflammatory state known as systemic inflammatory response syndrome to an immunosuppressed one, or compensatory anti-inflammatory response syndrome leading to increased complication rates (especially infections), length of hospital stay (LOS) and mortality [2]. Several studies associate a poor nutritional status to worse surgical outcome [3].

Between 20% and 53% of gynecological cancer patients have at least a mild malnutrition in USA and Australia, and even 62%–88% in India and Brazil. The risk of malnutrition is greatest in patients with ovarian cancer (OC) [4]. Furthermore, OC patients frequently need major abdominal surgery which is associated with a high risk of post-operative complications [5] and in many cases the nutritional status is inadequate to guarantee an optimal recovery to the surgical-induced stress [6].

The significant role of the immune system in cancer has led to the development of nutritional formulas containing defined quantities of essential amino acids, omega-3 fatty acids and nucleotides to provide immune support [7]. Immunonutrition is a valid strategy to stimulate patients' immune response, improve control of inflammatory response, increase protein synthesis and nitrogen balance after major surgery [8].

Due to their proven efficacy in decreasing complication rates and LOS, even in well-nourished patients, immune-modulating formulas have been recommended by European Society for Clinical Nutrition and Metabolism (ESPEN), American Society for Parenteral and Enteral Nutrition and other institutions as a grade A for patients undergoing major surgery of the gastro-intestinal tract and head-and-neck district [9,10].

Some recent studies focused on the use of peri-operative immunonutrition in gynecological cancer patients, but included few patients, affected by different neoplasms. Moreover, there are no official guidelines regarding the time and duration of formula intake [11-13].

Alterations in lymphocyte subpopulations and in lymphocyte function are common in cancer and could play a significant role in cancer treatment. Peripheral blood lymphocyte subpopulations may reflect host immune status and their number and proportions can be affected by a wide range of conditions including tumor and surgery [2,7,14].

Aim of this study is to evaluate the impact of pre-operative immunonutrition on the surgical outcome of OC patients, and on their nutritional, inflammatory and peripheral blood immune status.

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MATERIALS AND METHODS

A prospective study was performed at the Department of Gynecology and Obstetrics, Mauriziano Hospital, Torino, Italy, between September 2016 and April 2020. Patients with epithelial OC and surgical indication were enrolled. They were required to be at least 18 years old, be willing and able to give their informed consent and capable to feed orally.

The study was based on the experience developed in the same hospital about immunonutrition in colorectal oncological surgery. It was approved by the Institutional Review Board of the AO Ordine Mauriziano in 2016 and was submitted and approved by the Ethics Committee A.O.U. Città della Salute e della Scienza di Torino / AO Ordine Mauriziano / ASL Città di Torino (registration number: 688497). All patients signed an informed consent before they were enrolled in the study.

1. Study protocol

Before surgery, the patients' nutritional status was assessed by dedicated dietologists using the Malnutrition Universal Screening Tool (MUST) [15]. MUST is a 5-step screening tool to identify adults who are malnourished or at risk of malnutrition. The 5 steps include measuring height and weight to get a body mass index (BMI), noting percentage of unplanned weight loss, establishing acute disease effect; then scores of the 3 previous steps must be added to calculate the overall risk of malnutrition and a specific care plan must be developed (**Fig. S1**).

All of the patients received immune-enhancing enteral nutrition containing arginine, nucleotides and polyunsaturated fatty acids combined in a ready-to-drink-serving (Impact® Oral; Nestlé, Vevey, Switzerland) based on their score. One serving of this product (237 mL) contains 4.3 g of arginine, 430 mg nucleotides and 1.2 g eicosapentaenoic/docosahexaenoic omega-3 fatty acids, that are considered to be important components of immunonutrition. This product is commonly prescribed by dieticians and also recommended by international guidelines including ESPEN guidelines.

Patients with MUST scores of 0 or 1 (low or medium nutritional risk) received 2 servings per day for 5–7 days before surgery, while patients with MUST scores of 2 received 2 servings per day for 10 days before, based on the protocol developed and validated in our hospital for colorectal oncological surgery in accordance with a systemic review of high-risk surgical patients (**Fig. 1**) [16].

In early stages (International Federation of Gynecology and Obstetrics [FIGO] stage Ia–c) patients underwent cytoreductive surgery consisting in hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal staging, pelvic and para-aortic lymphadenectomy; in advanced disease also bowel resection, diaphragm or other peritoneal surface stripping, resection of suspicious and/or enlarged nodes (instead of systematic lymphadenectomy) could be necessary to remove all gross disease for a complete debulking. Single points (1 or 2) were assigned to each surgical procedure performed according to its complexity, in order to calculate the Surgical Complexity Score (SCS) developed by Aletti et al. [17]. A SCS of 0–3 was considered low, 4–7 moderate and ≥8 high.

2. Biochemical and hematological parameters

Biochemical and hematological monitoring was performed before and after the immunonutritional intake (the day before surgery). Lacking a consensus on the most

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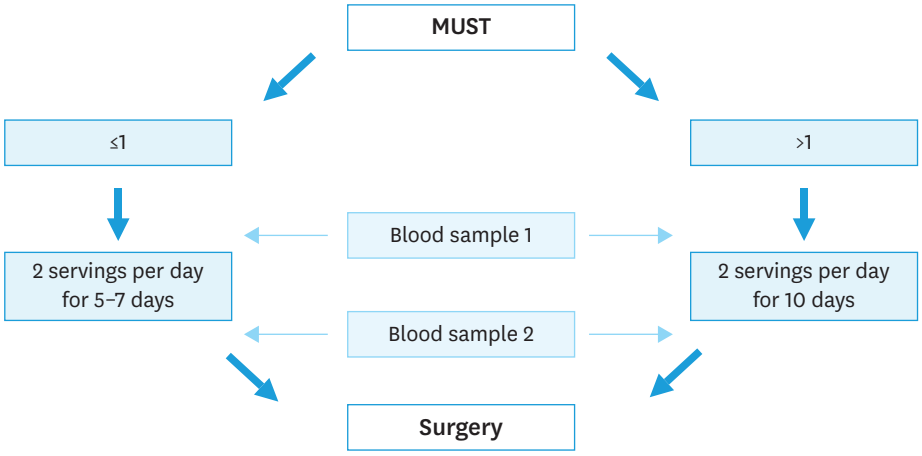

Fig. 1. Study protocol.
MUST, Malnutrition Universal Screening Tool.

performant biomarkers to monitor the effect of immunonutrition [18], we selected some nutritional (prealbumin, total serum proteins, creatinine), inflammatory (C-reactive protein [CRP]) and immunological (lymphocytes, granulocytes, monocytes) parameters.

Furthermore, peripheral blood lymphocyte subsets were analyzed with flow cytometry.

3. Clinical data and post-operative assessment

Patients' age, histotype, grading, FIGO stage, type of surgery, days of hospitalization and post-operative complications (according to Clavien-Dindo classification) were collected.

Post-operative data were compared with those of a continuous group consisting of all the patients surgically treated at the same center and by the same team in the 4 years (2013–2016) before the start of the study, without any additive nutritional support. Type of surgery, post-operative care standards and team of surgeons performing the procedures did not change over the time.

4. Statistical analysis

Biochemical, hematological and clinical values were compared using the student's t-test or the non-parametric Wilcoxon test when not normally distributed. Post-operative complications were analyzed with the χ^2 test. Statistical significance was set at $p<0.05$.

A multivariate logistic regression analysis was then performed to correct the effect of age, performance status and surgical complexity covariates on the outcome variables of length of stay and surgical complications.

The analysis was performed using the software SPSS statistics ver. 22.0 (IBM Inc., Chicago, IL, USA).

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RESULTS

A total of 42 patients with OC eligible for surgery were included in the prospective study (interventional group [IG]). The mean age was 63 years (range 40–82). Histotype, grading, FIGO stage, type and complexity of surgery are reported in **Table 1**.

According to MUST, 23 patients (54.8%) had a low risk of malnutrition (score 0), 11 (26.2%) an intermediate risk (score 1) and 8 (19%) a high risk (score 2).

After the immunonutritional intake, significant variations of prealbumin, creatinine and white blood cells were detected, while CRP resulted slightly decreased (**Table 2**). In the analysis of lymphocytes subsets, all T cell population, either cytotoxic and helper, had an increasing trend, in particular CD3-T lymphocytes (p=0.020), $CD3^{+}CD8^{+}$ cytotoxic T lymphocytes (p=0.046) and lymphocyte with HLA-DR expression (p=0.012); B lymphocytes were stable (**Table 3**).

Table 1. Patient characteristics

Characteristics	IG	CG	p-value
Mean age (range)	62.7 (40–82)	62.3 (32–78)	0.850
PS ≥1	16 (38.1)	15 (35.7)	0.290
Histotype			0.670
Serous	32 (76.2)	29 (69)	
Mucinous	3 (7.1)	2 (4.8)	
Endometrioid	1 (2.4)	4 (9.5)	
Clear cell	4 (9.5)	4 (9.5)	
Undifferentiated	2 (4.8)	3 (7.1)	
Grading			0.640
G1	4 (9.5)	2 (4.8)	
G2	2 (4.8)	3 (7.1)	
G3	36 (85.7)	37 (88.1)	
FI FIGO stage			0.710
I	7 (16.7)	8 (19)	
II	3 (7.1)	2 (4.8)	
III	19 (45.2)	23 (54.8)	
IV	13 (31)	9 (21.4)	
Type of surgery			0.650
PDS	27 (64.3)	25 (59.5)	
IDS	15 (35.7)	17 (40.5)	
No residual disease	27 (64.3)	28 (66.7)	0.820
SCS mean	4.4	5.2	0.190
Bowel resection	14 (33.3)	18 (42.8)	0.810

Values are presented as number of patients (%).
CG, control group; FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; IG, interventional group; PDS, primary debulking surgery; PS, performance status; SCS, Surgical Complexity Score.

Table 2. Biochemical and hematological monitoring before and after immunonutrition

Biochemical and hematological parameters	Average		p (Student's t)	p (Wilcoxon)
	Before	After		
Prealbumin (g/L)	0.19	0.21	0.050	0.050
CRP (mg/L)	36.20	30.90	0.566	0.334
Total protein (g/dL)	7.20	6.80	0.070	0.192
Creatinine (mg/dL)	0.64	0.79	0.080	0.020
White blood cells count ($\times 10^3$ µL)	6.76	8.75	0.040	0.001
Lymphocytes (%)	24.00	21.70	0.173	0.572
Granulocytes (%)	69.10	72.00	0.108	0.458
Monocytes (%)	6.90	6.30	0.122	0.154

CRP, C-reactive protein.

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Table 3. Peripheral blood lymphocyte subpopulations before and after immunonutrition

Lymphocyte subpopulations	Unit	Average		p (Student's t)	p (Wilcoxon)
		Before	After		
$CD3^+$ T lymphocytes	count/μL	976.40	1,084.20	0.054	0.020
$CD3^+CD4^+$ T helper lymphocytes	count/μL	654.00	685.28	0.139	0.152
$CD3^+CD8^+$ cytotoxic T lymphocytes	count/μL	348.17	386.79	0.081	0.046
$HLA\text{-}DR^+$ lymphocytes	count/μL	329.95	390.87	0.007	0.012
$CD3^+HLA\text{-}DR^+$ activated T lymphocytes	count/μL	135.51	145.77	0.704	0.733
$CD19^+$ B lymphocytes	count/μL	145.10	151.38	0.471	0.535
$CD20^+$ B lymphocytes	count/μL	177.56	144.42	0.510	0.406
$CD3^-CD56^+$ natural killer cells	count/μL	209.31	223.03	0.330	0.402
$CD3^+CD56^+$ natural killer T cells	count/μL	103.20	122.04	0.140	0.395

Table 4. Complications and length of hospital stay

Characteristics	IG	CG	p-value
Complications	15 (35.7)	24 (57.1)	0.060
Grade I	6 (40)	4 (16.6)	
Grade II	7 (46.6)	13 (54.1)	
Anemia	5	8	
Wound dehiscence	1		
Infection requiring antibiotic therapy	1	7	
Parenteral nutrition		1	
Grade III	2 (13.3)	5 (20.8)	
Pleural effusion	1	1	
Ureteral damage	1		
Thromboembolic complication		1	
Anastomotic leak		3	
Grade II–III complications	9 (21.4)	18 (42.9)	0.035
Length of hospital stay	7.5	9.2	0.009

Values are presented as number of patients (%).
CG, control group; IG, interventional group.

As shown in **Table 4**, 15 patients (35.7%) had post-operative complications, the majority (46.6%) being grade II, especially anemia requiring blood transfusion. Only 2 patients had grade III complications (pleural effusion and ureteral damage). The mean time of hospitalization was 7.5 days.

The same number of patients, with similar demographic, clinical and surgical characteristics (>0.05), were included in the control group (CG). The mean age was 62 years (range 37–78). Histotype, FIGO stage, grading, type and complexity of surgery are reported in **Table 1**.

The rate of post-operative complications did not significantly differ between the 2 groups (57.1% in CG vs. 35.7% in IG, p=0.06), however severe complications (grade II–III) were more frequent than in the immuno-nourished group (42.9% vs. 21.4%, respectively, p=0.035), as shown in **Table 4**. Seven patients in CG required antibiotic therapy due to infection, whereas only 1 patient in IG; anemia occurred in more patients in CG than in IG (8 vs. 5, respectively). Among grade III complications, anastomotic leak and thromboembolic event occurred only in CG.

The mean time of hospitalization was 9.2 days, indicating a significant longer stay compared to the immuno-nourished group (p=0.009).

At multivariate logistic regression analysis immunonutrition maintained statistically significance for length of stay (odds ratio [OR]=0.3; 95% confidence interval [CI]=0.1–0.8; p=0.010) and grade II–III complications (OR=0.4; 95% CI=0.1–0.9, p=0.049) (**Table 5**).

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Table 5. Logistic multivariate analysis to predict hospital stay and grade II–III complications

Characteristics	OR	95% CI	p-value
Length of stay (> median hospital stay)			
Age*	1.00	0.90–1.00	0.810
Ps†	0.60	0.20–1.60	0.350
scs†	1.50	1.20–2.00	0.001
Grade II–III complications	2.92	1.04–4.80	0.002
Immunonutrition	0.30	0.10–0.80	0.010
Grade II–III complications			
Age*	0.90	0.90–1.00	0.710
PS†	1.50	0.60–3.90	0.330
SCS†	1.40	1.10–1.70	0.003
Immunonutrition	0.40	0.10–0.90	0.049

CI, confidence interval; OR, odds ratio; PS, performance status; SCS, Surgical Complexity Score.
*Increase in 1 year; †Increase in 1-point score.

DISCUSSION

The ESPEN guidelines on nutrition in cancer patients recommend all the cancer patient should be screened for the risk or presence of malnutrition [1]. Literature evidences as 67%–70% of patients with OC are malnourished at the time of diagnosis [19]. In our series 45.2% were malnourished.

Surgical treatment of OC has a high rate of perioperative morbidity and malnutrition could worsen the postoperative course and prolong the hospital stay. In our study complete cytoreduction with no macroscopic residual disease was achieved in 27 patients of IG (64.3%) and in 28 of CG (66.7%). Mean SCS was 4.4 in IG and 5.2 in CG. Especially, 14 patients of IG (33.3%) and 18 of CG (42.8%) underwent bowel resection, underlining how cytoreductive surgery in OC mirror colo-rectal surgery.

We evaluated the nutritional status using MUST, however patients with OC frequently present ascites at the time of diagnosis which could alter BMI and weight loss, 2 parameters of MUST, hiding a malnutrition state [15-18]. For this reason, immune-enhancing nutrition has been also administered to patients with a score 0 for a shorter time.

As shown in **Table S1**, data about immunonutrition in OC are poor [11-13] and in most published studies patients with OC represent only a fraction of the sample (55% and 36%) [11,12], however the results obtained in gastro-intestinal surgery are encouraging [20]. It is unclear what is the correct timing of immunonutrition. Experimental and clinical data suggest that immune-enhancing nutrition should be started at least 3–5 days prior to surgery. In malnourished patients we prolonged treatment duration until 10 days. Some authors evaluated the immunonutrition also after surgery. We have chosen not to extend in postoperative time the immune-enhancing nutrition due to the poor adherence to treatment evidenced in other studies involving major abdominal surgery, often correlated with poor motivation, nausea and vomiting [13,16].

Our results demonstrated that adding pre-operative immunonutrition can mitigate surgical morbidity by reducing the length of hospitalization and severe postoperative complications. Hospital stay was shorter in IG than in CG (7.5 days vs. 9.2 days, p=0.009), this might be reflected in a cost reduction and a greater patient satisfaction. A similar result about length of stay was obtained by Celik et al. [12]. Hertlein et al. [13] did not evidence a reduction in

length of stay, maybe due to the small number of patients in each group and a poor adherence to postoperative immunonutrition intake.

Complexity of surgery influences the hospital stay and our data confirmed this correlation, however also immunonutrition showed an independent correlation (p=0.010).

The rate of post-operative complications decreased by 21.4% in our immune-nourished group, even if the difference was not statistically significant (p=0.060). Concerning the type of complications, we observed more severe complications requiring pharmacological, surgical or radiological treatment in the CG (CG 42.9% vs. IG 21.4%, p=0.035). Grade III complications, especially anastomotic leak, which requires a surgical reintervention, occurred mostly in patients who received standard nutrition. At logistic multivariate analysis immunonutrition was independently associated with a decreased risk of grade II–III complications (p=0.049).

In our study 7 patients of the CG had infections requiring antibiotic therapy, whereas only one patient in the IG, confirming a decreasing effect of immunonutrition (IG 2.4% vs. CG 16.7% p=0.060). A positive effect by immunonutrition on infectious complications was expected, as demonstrated by previous studies on gastro-intestinal and OCs [11,21,22].

According to literature, prealbumin and total protein can be indicators of the patient nutritional status. Furthermore, prealbumin concentration seems to have a prognostic importance in women with OC, inversely related to tumor volume [23]. In our study total protein level did not show any variation, mean prealbumin level slightly increased from 0.19 g/L to 0.21 g/L after immunonutrition even if not significantly (p=0.050), as instead reported by Celik et al. [12]. Differently from the study of Celik et al. [12], we analyzed the variation of laboratory biomarkers before and after the enteral nutrition emphasizing the impact of immunonutrition on biochemical parameters.

Omega-3-fatty acids, arginine and nucleotides have been shown to be associated with immunological benefits. The addition of these compounds in preoperative enteral nutrition could relieve inflammatory response and enhance host immunity by increasing T cells, immunoglobulins and natural killer cells in peripheral blood sample [20]. Also tumor infiltrating lymphocytes (TILs), which seem to be related to better prognosis in OC [24], resulted increased in surgical specimens of immune-nourished patients with colorectal cancer [25].

Influence on inflammatory response has been evaluated dosing CRP before and after immunonutrition. Data showed a decreasing trend of CRP in our cohort, from 36.2 mg/L to 30.9 mg/L after immunonutrition, a result in line with the study of Giger et al. [26].

Only few studies reported the effect of immunonutrition on immune system and with inconsistent results. In our cohort white blood cells and all subsets of T lymphocytes had an increasing trend, in particular $CD3^+$ T lymphocytes, $CD3^+CD8^+$ cytotoxic T lymphocytes and lymphocyte with HLA-DR expression, while B lymphocytes remained stable. The trend of T lymphocytes, especially $CD3^+CD8^+$ cytotoxic ones, could be explained as an increased mobilization of T lymphocytes into the blood circulatory system. Other studies analyzed white blood cell count and $CD4^+$ T cells reporting an increase of the first, but no significant variation of $CD4^+$ T cells [12,21]. Different types of $CD4^+$ effector cells are produced during immune system activation. Among these, CD4 regulatory T cells are associated with the inhibition of host defence both in the tumor microenvironment and in the inflammatory

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response after surgery, CD8 T cells play a central role in the anti-tumor immune response because of their cytotoxic effect [2,7].

Immunonutrition is a field of research in the perioperative care of gynecologic oncological patient [27]. In our experience preoperative immune-enhancing enteral nutrition improve the surgical outcome of OC patients. The low number of patients and the retrospective CG limit our study, but at our knowledge it's the largest reported one including only patients with OC. Other published studies enrolled patients with both ovarian and endometrial cancer or benign pathologies [11,12]; this heterogenous population could respond differently to immunonutrition and make it difficult to analyze length of hospitalization and postoperative complications. Another limitation could be represented by the intake of immune-enhancing oral formula in an outpatient setting, making difficult to assess the compliance to immunonutrition among patients of the IG. However, all the patients declared to have taken all the supplements recommended. Lastly, even if patients of the 2 groups were operated at the same centre and by the same surgical team, they were treated in 2 different periods (2016–2020 for the IG and 2013–2016 for the CG).

Immunotherapy is still under investigation in OC [28]. We detected an increase of $CD3^+CD8^+$ cytotoxic T lymphocytes after immunonutrition that could enhance the anti-tumor immune response. Further studies are necessary to investigate the effect of immunonutrition on inflammatory response, TILs regulation, and host immunity. We are analyzing other lymphocyte subsets that will be eventually reported. The impact of pre-operative immunonutrition on survival has not yet been investigated in literature, our data did not permit a survival analysis due to the short follow up time, but in the next years it could be interesting to perform this analysis with an adequate longer follow up time.

Immunonutrion should be further investigated and implemented to modulate the inflammatory response and stimulate the host immune response. It could be included in the perioperative management of OC patients to improve their outcome.

SUPPLEMENTARY MATERIALS

Table S1

Results of studies on immunonutrition in gynecological patients

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Fig. S1

Malnutrition Universal Screening Tool.

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REFERENCES

1. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36:11-48.
PUBMED | CROSSREF

2. Calder PC. Immunonutrition in surgical and critically ill patients. Br J Nutr 2007;98 Suppl 1:S133-9.
PUBMED | CROSSREF
3. Mignini EV, Scarpellini E, Rinninella E, Lattanzi E, Valeri MV, Clementi N, et al. Impact of patients nutritional status on major surgery outcome. Eur Rev Med Pharmacol Sci 2018;22:3524-33.
PUBMED | CROSSREF
4. Obermair A, Simunovic M, Isenring L, Janda M. Nutrition interventions in patients with gynecological cancers requiring surgery. Gynecol Oncol 2017;145:192-9.
PUBMED | CROSSREF
5. Giannopoulos T, Butler-Manuel S, Taylor A, Ngeh N, Thomas H. Clinical outcomes of neoadjuvant chemotherapy and primary debulking surgery in advanced ovarian carcinoma. Eur J Gynaecol Oncol 2006;27:25-8.
PUBMED
6. Kathiresan AS, Brookfield KF, Schuman SI, Lucci JA 3rd. Malnutrition as a predictor of poor postoperative outcomes in gynecologic cancer patients. Arch Gynecol Obstet 2011;284:445-51.
PUBMED | CROSSREF
7. Prieto I, Montemuiño S, Luna J, de Torres MV, Amaya E. The role of immunonutritional support in cancer treatment: current evidence. Clin Nutr 2017;36:1457-64.
PUBMED | CROSSREF
8. Mariette C. Immunonutrition. J Visc Surg 2015;152 Suppl 1:S14-7.
PUBMED | CROSSREF
9. Zhang X, Chen X, Yang J, Hu Y, Li K. Effects of nutritional support on the clinical outcomes of well-nourished patients with cancer: a meta-analysis. Eur J Clin Nutr 2020;74:1389-400.
PUBMED | CROSSREF
10. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. Clin Nutr 2006;25:224-44.
PUBMED | CROSSREF
11. Chapman JS, Roddy E, Westhoff G, Simons E, Brooks R, Ueda S, et al. Post-operative enteral immunonutrition for gynecologic oncology patients undergoing laparotomy decreases wound complications. Gynecol Oncol 2015;137:523-8.
PUBMED | CROSSREF
12. Celik JB, Gezginç K, Ozçelik K, Celik C. The role of immunonutrition in gynecologic oncologic surgery. Eur J Gynaecol Oncol 2009;30:418-21.
PUBMED
13. Hertlein L, Zeder-Göß C, Fürst S, Bayer D, Trillsch F, Czogalla B, et al. Peri-operative oral immunonutrition in malnourished ovarian cancer patients assessed by the nutritional risk screening. Arch Gynecol Obstet 2018;297:1533-8.
PUBMED | CROSSREF
14. Blum KS, Pabst R. Lymphocyte numbers and subsets in the human blood. Do they mirror the situation in all organs? Immunol Lett 2007;108:45-51.
PUBMED | CROSSREF
15. National Institute for Health and Clinical Excellence (UK). Nutrition support in adults. NICE quality standard 24. London: National Institute for Health and Clinical Excellence; 2012.
16. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enteral Nutr 2010;34:378-86.
PUBMED | CROSSREF
17. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol 2007;197:676.e1-7.
PUBMED | CROSSREF
18. Forget P, Echeverria G, Giglioli S, Bertrand B, Nikis S, Lechat JP, et al. Biomarkers in immunonutrition programme, is there still a need for new ones? A brief review. Ecancermedicalscience 2015;9:546.
PUBMED | CROSSREF
19. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. Am J Clin Nutr 2008;87:1678-85.
PUBMED | CROSSREF
20. Song GM, Liu XL, Bian W, Wu J, Deng YH, Zhang H, et al. Systematic review with network meta-analysis: comparative efficacy of different enteral immunonutrition formulas in patients underwent gastrectomy. Oncotarget 2017;8:23376-88.
PUBMED | CROSSREF

21. Niu JW, Zhou L, Liu ZZ, Pei DP, Fan WQ, Ning W. A systematic review and meta-analysis of the effects of perioperative immunonutrition in gastrointestinal cancer patients. Nutr Cancer 2021;73:252-61.
PUBMED | CROSSREF
22. Rinninella E, Fagotti A, Cintoni M, Raoul P, Scaletta G, Quagliozzi L, et al. Nutritional interventions to improve clinical outcomes in ovarian cancer: a systematic review of randomized controlled trials. Nutrients 2019;11:1404.
PUBMED | CROSSREF
23. Mählck CG, Grankvist K. Plasma prealbumin in women with epithelial ovarian carcinoma. Gynecol Obstet Invest 1994;37:135-40.
PUBMED | CROSSREF
24. Li J, Wang J, Chen R, Bai Y, Lu X. The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. Oncotarget 2017;8:15621-31.
PUBMED | CROSSREF
25. Caglayan K, Oner I, Gunerhan Y, Ata P, Koksal N, Ozkara S. The impact of preoperative immunonutrition and other nutrition models on tumor infiltrative lymphocytes in colorectal cancer patients. Am J Surg 2012;204:416-21.
PUBMED | CROSSREF
26. Giger U, Büchler M, Farhadi J, Berger D, Hüsler J, Schneider H, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol 2007;14:2798-806.
PUBMED | CROSSREF
27. Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer 2019;29:651-68.
PUBMED | CROSSREF
28. Kandalaft LE, Odunsi K, Coukos G. Immune therapy opportunities in ovarian cancer. Am Soc Clin Oncol Educ Book 2020;40:1-13.
PUBMED | CROSSREF