



Impact of Sentinel Node Mapping in Decreasing the Risk of Lymphocele in Endometrial Cancer

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ABSTRACT

Objective. Due to the growing evidence of sentinel lymph node (SLN) mapping in endometrial cancer (EC), our aim was to evaluate the impact of SLN mapping and other clinical-pathological variables in the risk of developing lymphocele.

Methods. We retrospectively analyzed a series of patients with ECs who underwent lymph node staging with SLN mapping with or without systematic pelvic \pm para-aortic lymphadenectomy from November 2012 to January 2020. The lymphocele diagnosis was performed by computed tomography or magnetic resonance imaging.

Results. Of 348 patients included, 178 underwent SLN mapping only and 170 underwent SLN mapping and systematic lymphadenectomy (46.5% pelvic only; 53.5% pelvic and para-aortic). Seventy-three (21%) patients had open surgery and 275 (79%) had a minimally invasive approach. After a median follow-up of 25.4 months, the overall prevalence of lymphocele was 8.6% ($n = 30$), with 29 cases in a pelvic location. Lymphocele was found in 3.4% ($n = 6/178$) of patients submitted to SLN mapping only, compared with 14.1% ($n = 24/170$) among those who underwent SLN with lymphadenectomy ($p = 0.009$). Among those patients with lymphocele, seven (23.3%) were symptomatic and five (16.6%) required drainage. All

symptomatic cases occurred in lymphoceles larger than 4 cm ($p = 0.001$). Neither resected lymph node count nor the type of systematic lymphadenectomy were related to the presence of lymphocele. Systematic lymphadenectomy was the only factor that emerged as a risk factor for the presence of lymphocele in multivariate analysis (odds ratio 3.68, 95% confidence interval 1.39–9.79; $p = 0.009$).

Conclusions. Our data suggest that SLN mapping independently decreases the risk of lymphocele formation compared with full lymphadenectomy in EC.

Since the publication of the Gynecologic Oncology Group (GOG) 33 study, endometrial cancer (EC) staging shifted from a clinical to a surgical approach that includes total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy, with or without para-aortic lymphadenectomy.¹ Additionally, the current staging system considers lymph node metastasis as stage III disease,^{2,3} with further guidance for adjuvant therapy. However, systematic lymphadenectomy is associated with increased costs, the addition of surgical time, and morbidity, with no evident survival benefits after two randomized controlled trials.^{4,5}

Sentinel lymph node (SLN) mapping has emerged as an accurate alternative between no staging and full lymph node dissection, and the National Comprehensive Cancer Network (NCCN) have been recommending this procedure as an alternative since 2014.⁶ One of the major complications of lymphadenectomy in gynecological malignancies is due to lymphatic disruption, such as lymphedemas and lymphoceles. Lymphoceles are cystic collections of lymphatic content without an epithelial lining tissue that are

usually neglected and occur between 4 weeks to 1 year after surgery. When symptomatic (pelvic pain, venous thrombosis, hydronephrosis, and infection), they can impact women's quality of life and even delay a recommended adjuvant treatment.

Some randomized studies have evaluated the impact of surgical interventions that aimed to reduce the prevalence of lymphoceles, including the use of biological glues, drainage of the peritoneal cavity, peritoneum closure, use of clips, and ultrasonic energy, however all studies failed to demonstrate a clear benefit.^{7–10} Moreover, data on the risk factors for lymphocele are lacking.

Due to the growing evidence of SLN mapping in EC, we hypothesized that SLN mapping would decrease the risk of lymphocele formation compared with lymphadenectomy in EC. Moreover, our aim was to also evaluate the impact of other clinical and pathological variables in the risk of developing postoperative lymphocele.

METHODS

Patients

We retrospectively analyzed 348 patients who had surgical staging for EC in the AC Camargo Cancer Center from November 2012 to January 2020. All patients had total hysterectomy with bilateral salpingo-oophorectomy with SLN mapping alone or associated with systematic pelvic \pm para-aortic lymphadenectomy. Cases with extrauterine disease or previous pelvic radiotherapy were excluded.

The clinical and pathological data were retrieved from our database and the Institutional Review Board approved the study (#120563). The criteria for the addition of systematic lymphadenectomy were mainly due to the presence of high-risk tumors, considered as those with high-grade tumor (endometrioid grade 3 and non-endometrioid histologies—serous, clear cell, or carcinosarcoma), deep myometrial invasion ($\geq 50\%$), or cervical invasion. Of the 178 cases that had only SLN mapping, 26 (14.6%) had unilateral detection. Due to the low-risk factors found in frozen section, these patients did not have further lymphadenectomy and were included in the SLN-only group.

Intraoperative Lymphatic Mapping

For the SLN protocol, all patients received patent blue dye or indocyanine green (ICG) at 1.25 mg/mL dilution. These compounds were administered by cervical injection only (a total of 4 mL of patent blue dye or ICG)—1 mL superficially and 1 mL deeply (1 cm) at 3 and 9 o'clock.

The first blue or green lymph nodes directly from uterine lymphatic drainage were resected and considered as SLNs.

Pathological Evaluation

A gynecological pathologist prospectively evaluated the pathological specimens (LDB). The SLNs were examined by immunohistochemistry (IHC) when the hematoxylin and eosin (H&E) stain was negative. Briefly, SLNs were serially sectioned every 2 mm and stained with H&E at three levels of the tissue block. If the sample was negative, a pan-cytokeratin stain was performed at each of the three levels. SLNs were classified as (1) macrometastases: tumor ≥ 2.0 mm; (2) micrometastases: tumor cell aggregates between 0.2 and 2.0 mm; (3) isolated tumor cells (ITCs): individual tumor cells or aggregates ≤ 0.2 mm; or (4) negative. All lymph nodes with ITCs and microscopic or macroscopic metastases were considered positive. Non-SLNs were reported as positive or negative for metastasis, based on routine sectioning and examination of a single H&E-stained slide per a standard protocol.

Lymphadenectomy

Pelvic lymphadenectomy was defined as the resection of lymph nodes in the region of the external and internal iliac vessels and obturator fossa. Inferiorly, the anatomical limits were the circumflex vein; superiorly, the bifurcation of the common iliac vessels; medially, the umbilical artery; laterally, the genitofemoral nerve; and deeply, the obturator nerve. Access to the retroperitoneum was performed by opening the peritoneum along the root of the mesentery, and para-aortic lymphadenectomy was performed up to the inferior mesenteric artery (IMA) or renal vessels. After this procedure, the peritoneal cavity remained opened in all cases. Six gynecologic oncologists who have been part of the same group for the last 10 years performed all procedures.

Lymphocele Diagnosis

Lymphoceles were considered cystic collections measurable in three dimensions, regardless of format, with or without internal septations along the pelvic vessels or retroperitoneum and diagnosed by imaging studies (computed tomography or magnetic resonance imaging). We considered the largest diameter (cm) as the size of the lymphocele. All patients had follow-up with pelvic and abdominal imaging examinations every 3–4 months for the first 2 years.

Patients with symptoms were instructed to go to the emergency department and were subsequently submitted to imaging tests. Symptomatic cases received treatment,

which could be simple analgesia or percutaneous image-guided drainage and antibiotics, if indicated. As we found lymphocele in patients before the initiation of adjuvant radiotherapy, we excluded radiotherapy as a risk factor in the analysis.

Statistical Analysis

A database was constructed using SPSS version 20.0 for Mac (IBM Corporation, Armonk, NY, USA). The Chi-square and Fisher's exact tests were used to analyze the correlations between categorical variables, and the Mann-Whitney U test was used for non-parametric correlations. Risk factors for lymphocele were assessed using logistic regression for univariate and multivariate analysis using a stepwise model. For all tests, a p -value < 0.05 was considered to be significant.

RESULTS

The clinical and pathological variables are summarized in Table 1. The SLN mapping was performed alone in 178 (51.1%) patients and was associated with lymphadenectomy in 170 (48.9%) patients. Seventy-three (21%) cases had open surgeries and 275 (79%) used a minimally invasive approach—183 (52.6%) laparoscopic and 92 (26.4%) robotically assisted. The overall SLN detection rate was 88.8%, and SLNs were bilateral in 69.5% of patients. The median SLN was 2 (range 2–8). Patent blue was used in 258 (74.1%) patients, and ICG was used in 85 (24.4%) and 5 cases (1.4%). The SLN sensitivity, negative predictive value, false negative rate, and false negative predictive value were 91.1%, 99.2%, 8%, and 0.8%, respectively.

Regarding the type of systematic lymphadenectomy, 79 (46.5%) patients underwent pelvic-only lymphadenectomy, while 91 (53.5%) patients underwent pelvic and para-aortic lymphadenectomy—24 (26.3%) up to the IMA and 67 (73.6%) up to the renal vessels. The median number of dissected pelvic lymph nodes was 23 (range 8–69) and the median number of para-aortic lymph nodes was 15 (range 3–68), with an overall positive lymph node rate of 21.8%. After a median follow-up of 25.4 months (range 2–64), the prevalence of lymphocele was 8.6% (30/348) and the median time between surgery and lymphocele diagnosis was 4.7 months (range 0.8–22.3). The median follow-up time did not differ between patients with SLN only compared with patients with SLN and lymphadenectomy, i.e. 25.7 and 25.3 months, respectively ($p = 0.13$). Additionally, the median lymphocele size was 4.4 cm (range

1.5–15), they were mainly localized in the pelvic area (96.7%), and were unilateral (90%). Figure 1 depicts the flowchart of patients with lymphocele.

Among the 30 patients who presented with lymphocele, seven (23.3%) were symptomatic and the median time for diagnosis of the symptomatic lymphoceles was shorter than for asymptomatic lymphoceles (3.1 vs. 4.9 months), but with no statistical difference ($p = 0.9$). The most common symptoms were isolated pelvic pain ($n = 3$), pelvic pain and hydronephrosis ($n = 1$), pelvic pain and fever ($n = 2$), and vaginal discharge ($n = 1$). Due to symptoms, five cases had percutaneous drainage and one case required a second drainage. Moreover, the drain was withdrawn after a median time of 8 days (range 2–23). The only factor related to the presence of symptoms was the size of the lymphocele; however, all symptomatic cases (7/30) had a lymphocele size larger than 4 cm ($p = 0.001$). Table 2 reports the characteristics of the 30 patients who developed lymphocele.

In univariate analysis, deep myometrial invasion (odds ratio [OR] 3.17, 95% confidence interval [CI] 1.46–6.88; $p = 0.003$) and systematic pelvic lymphadenectomy (OR 4.71, 95% CI 1.87–11.84; $p = 0.001$) were the only factors related to lymphocele formation. The addition of para-aortic lymphadenectomy (OR 1.18, 95% CI 0.49–2.84; $p = 0.70$), and the total number of resected lymph nodes assessed as a continuous variable ($p = 0.93$), did not impact the risk of lymphocele. In multivariate analysis, the only variable that remained a risk for lymphocele was systematic lymphadenectomy (OR 3.69, 95% CI 1.39–9.79; $p = 0.009$) [Table 3]. Additionally, the presence of lymphocele was found in 3.4% ($n = 6/178$) of patients submitted to SLN-only mapping compared with 14.1% ($n = 24/170$) among those who underwent SLN mapping with lymphadenectomy ($p = 0.009$).

DISCUSSION

Lymphoceles are liquid collections without a true epithelial lining that arise after the rupture of lymphatic vessels, usually after lymph node dissection. Lymphocele should be considered as surgical morbidity; the incidence ranges from 10% to 47% of cases and lymphocele is mostly reabsorbed in up to 8 weeks.¹¹ In symptomatic cases, clinical or surgical intervention could be necessary. In our series, we found a relatively low overall prevalence rate (8.6%) of lymphocele after lymph node staging, usually unilateral and localized in the pelvis. However, nearly one-quarter of lymphocele cases were symptomatic, and, ultimately, 0.2% of cases required percutaneous drainage, yielding lower rates compared with previously reported series.^{11,12} However, the presence of symptoms correlated

TABLE 1 Clinical and pathological characteristics of the 348 patients with endometrial cancer submitted to sentinel lymph node mapping with or without lymphadenectomy

Variable		SLN only [n = 178] (%)	SLN and lymphadenectomy [n = 170] (%)	Total 348 (%)	p-Value
Age, years [median (range)]		59.1 (35–86)	60.2 (28–84)	60 (28–86)	0.49
Body mass index, kg/m ² [median (range)]		29.3 (18–53.1)	27.5 (16.9–54.9)	28.6 (16.9–54.9)	0.11
Lymphocele	No	172 (96.6)	146 (85.9)	318 (91.4)	< 0.001
	Yes	6 (3.4)	24 (14.1)	30 (8.6)	
ASA	1 and 2	155 (87.1)	149 (87.6)	304 (87.4)	0.87
	3	23 (12.9)	21 (12.4)	44 (12.6)	
Surgical approach	Open	24 (13.5)	49 (28.8)	73 (21.0)	0.02
	Laparoscopy	102 (57.3)	81 (47.6)	183 (52.6)	
	Robotic-assisted	52 (29.2)	40 (23.5)	92 (26.4)	
Tracer utilized	Patent blue	109 (61.2)	149 (87.6)	258 (74.1)	< 0.001
	Indocyanine green	66 (37.1)	19 (11.2)	85 (24.4)	
	Both	3 (1.7)	2 (1.2)	5 (1.4)	
Type of lymphadenectomy	Pelvic	–	79 (46.5)	79 (46.5)	–
	Para-aortic up to IMA	–	24 (14.1)	24 (14.1)	
	Para-aortic up to RV	–	67 (39.4)	67 (39.4)	
SLN metastasis	No	153 (94.4)	114 (78.6)	267 (87)	< 0.001
	ITC	2 (1.2)	5 (3.4)	7 (2.3)	
	Micrometastases	4 (2.5)	13 (9.0)	17.5 (5.5)	
	Macrometastases	3 (1.9)	13 (9.0)	16 (5.2)	
Histologic type	Endometrioid	164 (92.1)	122 (71.8)	286 (82.6)	< 0.001
	Serous	4 (2.2)	19 (11.2)	23 (6.6)	
	Clear cell	2 (1.1)	2 (1.2)	4 (1.1)	
	Carcinosarcoma	1 (0.6)	10 (5.9)	11 (3.2)	
	Other ^a	7 (4.0)	17 (9.9)	24 (6.9)	
FIGO Stage	IA	161 (90.5)	93 (54.7)	254 (73)	
	IB	6 (3.4)	30 (17.6)	36 (10.3)	
	II	3 (1.7)	7 (4.1)	10 (2.9)	
	IIIA	–	7 (4.1)	7 (2.0)	
	IIIB	2 (1.1)	1 (0.6)	3 (0.9)	
	IIIC1	6 (3.4)	26 (15.3)	32 (9.1)	
	IIIC2	–	6 (3.5)	6 (1.7)	
Histological grade	1	114 (64)	53 (31.2)	167 (48)	< 0.001
	2	43 (24.2)	43 (25.3)	43 (25.3)	
	3	21 (11.8)	74 (43.5)	95 (27.3)	
Presence of LVSI	No	166 (92.1)	120 (70.6)	286 (82.2)	0.025
	Yes	12 (7.9)	50 (29.4)	62 (17.8)	
Myometrial invasion	< 50%	167 (93.8)	107 (63.0)	274 (78.7)	< 0.001
	≥ 50%	11 (6.2)	63 (37.0)	74 (21.3)	

Data are expressed as *n* (%) unless otherwise specified

SLN sentinel lymph node, ASA American Society of Anesthesiologists risk classification, IMA inferior mesenteric artery, RV renal vessels, ITC isolated tumor cells, LVSI lymphovascular space invasion, FIGO International Federation of Gynecology and Obstetrics

^aIncludes mixed histological types and dedifferentiated carcinoma

with the size of lymphocele, and the only variable that remained as an independent risk factor for lymphocele formation was systematic lymphadenectomy.

The literature is very scarce regarding lymphatic complications after lymph node dissection, especially for lymphocele formation. In 1955, Mori¹³ described the first

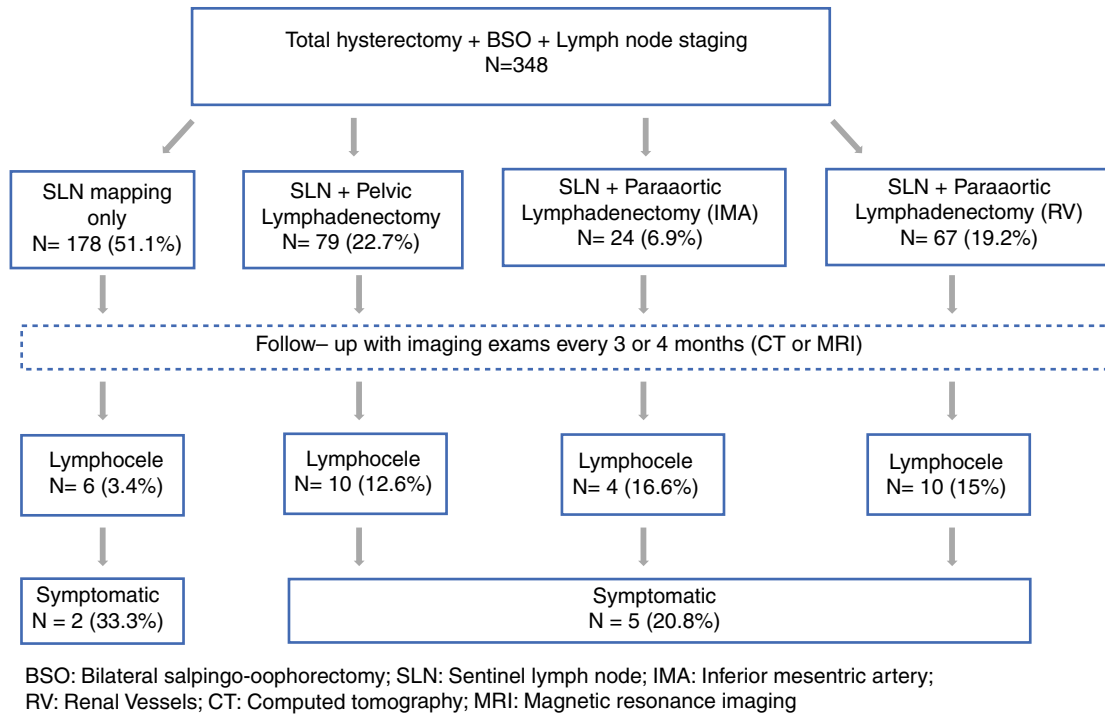


FIG. 1 Patients with endometrial cancer submitted to lymph node staging

TABLE 2 Clinical and pathological characteristics of the 30 patients with endometrial cancer who developed lymphoceles after lymph node staging

Variable	No. of patients	(%)	
Lymphocele size, cm [median (range)]	4.4 (1.5–15.0)		
Time for diagnosis, months [median (range)]	4.7 (0.8–22.3)		
Time length of lymphocele drainage, days [median (range)]	8.0 (2.0–23.0)		
Laterality			
	Unilateral	27	90
	Bilateral	3	10
Location			
	Pelvic	29	96.7
	Para-aortic	1	3.3
Presence of symptoms			
	No	23	76.7
	Yes	7	23.3
Drainage of lymphocele			
	No	25	83.3
	Yes	5	16.7
Type of surgery			
	Open	11	36.7
	Laparoscopy	10	33.3
	Robotic-assisted	9	30
Type of lymphadenectomy			
	Pelvic	10	33.3
	Para-aortic up to IMA	4	13.3
	Para-aortic up to RV	10	33.3
	SLN only	6	20

IMA inferior mesentery artery, RV renal vessels, SLN sentinel lymph node

series of lymphocele in gynecological cancer, with a prevalence of 48.5%. More recently, Zikan et al.¹⁴ evaluated the presence of lymphocele after pelvic ± para-aortic

lymph node dissection in a series of 800 patients with gynecological neoplasms and reported an overall incidence

TABLE 3 Univariate and multivariate analysis of predictive factors for lymphocele formation (logistic regression)

Variables	Univariate analysis					Multivariate analysis*		
	Category	<i>n</i>	OR	(95% CI)	<i>p</i> -Value	OR	(95% CI)	<i>p</i> -Value
Myometrial invasion	< 50%	274	1.0	Reference				
	≥ 50%	74	3.17	(1.46–6.88)	0.003	1.96 ^a	(0.86–4.48)	0.11
Lymphadenectomy	No	178	1.0	Reference				
	Yes	170	4.71	(1.87–11.84)	0.001	3.69	(1.39–9.79)	0.009
BMI, kg/m ²	< 30	213	1.0	Reference				
	≥ 30	135	1.42	(0.67–3.02)	0.35	–	–	–
Surgical approach	MIS	275	1.0	Reference				
	Open	73	2.15	(0.95–4.83)	0.06	1.63 ^a	(0.70–3.71)	0.26
Histological type	Endometrioid	286	1.0	Reference				
	Non-endometrioid	62	2.19	(0.95–5.05)	0.06	1.47 ^a	(0.62–3.51)	0.37
LVSI	No	286	1.0	Reference				
	Yes	62	1.77	(0.75–4.20)	0.19	–	–	–
Positive lymph nodes	No	300	1.0	Reference				
	Yes	48	2.01	(0.78–5.17)	0.14	–	–	–
Para-aortic lymphadenectomy	No	77	1.0	Reference				
	Yes	93	1.18	(0.49–2.84)	0.70	–	–	–
Total lymph nodes resected	Continuous		0.99	(0.97–1.02)	0.93			

OR odds ratio, CI confidence interval, BMI body mass index, MIS minimally invasive surgery, LVSI lymphovascular space invasion

^aAdjusted for lymphadenectomy

of 20.1%. For the 307 cases with EC, lymphocele was reported in 26.7% of cases and 30.4% of cases were symptomatic.

The only series that addressed lymphocele formation after SLN mapping for EC was reported by Geppert et al.¹⁵ The authors evaluated lymphatic complications in 181 patients undergoing SLN mapping ± robotically assisted lymphadenectomy in EC. With a follow-up of at least 20 months, the prevalence of lymphocele was 13.3% after systematic lymphadenectomy, compared with 2.6% in patients who underwent SLN biopsy only ($p = 0.02$). Similarly, after a median follow-up of 25.4 months, our results showed a lymphocele rate of 14.1% for the lymphadenectomy group, compared with 3.4% for the SLN mapping group ($p = 0.009$), with an OR of 3.69 (95% CI 1.39–9.79) after multivariate analysis.

Regarding the extension of systematic lymph node dissection, Volpi et al.¹⁶ published a series of 249 women who underwent systematic lymphadenectomy in EC, and found no differences in the lymphocele rates in relation to lymph node count (≥ 15 vs. < 15 ; $p = 0.07$). However, the addition of para-aortic node dissection increased the risk of lymphocele compared with a pelvic procedure alone (60% vs. 40%; $p = 0.001$). Additionally, Kim et al.¹⁷ suggested that the number of lymph nodes dissected increased the lymphocele formation (≥ 23 vs. < 23 ; $p = 0.03$).

Conversely, Achouri et al.¹² as well as our series, did not demonstrate an increased risk of lymphocele formation, neither for the addition of para-aortic node dissection nor for lymph node count.

We also evaluated other possible clinical and pathological factors as predictors of lymphocele formation, such as body mass index, type of surgical access, and pathological variables. Of these, only deep myometrial invasion was related to a higher risk of lymphocele; however, it did not emerge as a risk factor after adjustment for type of node staging, probably due to systematic lymphadenectomy in cases with deep myometrial invasion.

Regarding surgical approach, Ghezzi et al.¹⁸ reported lower lymphocele rates in patients undergoing minimally invasive surgery compared with open surgery in EC. In contrast, we did not find surgical approach to be a risk factor for lymphocele, and, curiously, all patients who required drainage of the collection also underwent minimally invasive surgery. Some studies suggested that peritoneum closure, postoperative drainage, and biological glues could be modifying factors for lymphocele formation; however, their effectiveness in preventing lymphocele has already been tested and have not confirmed by randomized trials.^{7–10}

Although this study may be limited by the inherent biases of a retrospective, single-institution design, to our knowledge this is the largest cohort that has evaluated lymphocele in patients undergoing SLN mapping for EC, and may hence contribute valuable data.

CONCLUSION

Our data support the hypothesis that SLN mapping independently decreases the risk of lymphocele formation compared with full lymphadenectomy in EC.

AUTHOR CONTRIBUTIONS Study concept and design: GB, HM, LBF, TPD. Data acquisition: TPD, CCF, GB, HM, BTG, JNM, EK. Quality control of data: GB, LYK, BTG, EK. Data analysis and interpretation: GB, TPD, LBF, JNM. Statistical analysis: GB, TPD. Manuscript preparation and editing: TPD, GB. Manuscript review: All authors.

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