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EDITORIAL

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Le 1er Salon JFMO-Mémorial Pr.Merouane BOUKRISSA, pari tenu !

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Un des objectifs majeur qui tenait à cœur aux membres de la rédaction du journal était l'organisation du premier salon JFMO à la mémoire de Feu le Professeur Merouane BOUKRISSA, un des membres fondateurs du journal. En effet, le Journal de la Faculté de Médecine d'Oran (JFMO) & le Réseau Education Qualité et Sécurité des Soins Respiratoires ont organisé les 23 & 24 mai 2024 à l'hôtel 2H, Oran, le 1er salon JFMO-Mémorial Pr Merouane BOUKRISSA, en communication avec l'actualité pneumologique.

Associer la rédaction scientifique à la pratique pneumologique n'est pas anodin, dans la mesure où ces deux entités se complètent et s'entremêlent. En effet, c'est grâce à la pratique médicale que les chercheurs hospitalo-universitaires publient leurs travaux originaux, et inversement, c'est la publication scientifique qui permet à ces chercheurs de renforcer leur connaissance et d'être à jour. A travers le 1er salon de JFMO, il était question de célébrer la 16ème édition du journal, c'est dire sept années d'existence, et enfin une visibilité nationale et internationale. De même, la rédaction a rendu un vibrant hommage à un des principaux membres fondateurs, en l'occurrence, Feu le Professeur Merouane BOUKRISSA, et a mis en avant un des objectifs du journal, l'initiation de nos jeunes médecins à l'écriture et à la publication scientifique *via* des conférences et des ateliers pratiques.

L'intégration de JFMO à l'Algerian Scientific Journal Platform (ASJP) en 2019, a permis sa pénétration nationale. La visibilité internationale s'est exprimée dès 2021, après 4 ans d'édition, par l'adhésion à Crossref, organisation américaine à but non lucratif qui joue le rôle d'une agence d'enregistrement et de registre des Digitals Object Identifier/DOI (identifiant objet numérique). Cette agence permet l'identification rapide des articles scientifiques et une large diffusion de la connaissance scientifique. En outre, le processus de l'évaluation « par les pairs » (Peer Review), longtemps éclipsé et sans aucune motivation, malgré son apport pertinent à la publication scientifique, se voit aujourd'hui gratifié.

En effet, en 2016, deux reviewers, Giacomo Bellani and Robert fruscio créent Reviewer Credits, une plateforme indépendante dans l'optique de mettre en place un système de récompense ou de gratification des reviewers. Selon les fondateurs, l'effort et l'engagement doivent être récompensés et reconnus. Notre membership à cette plateforme a motivé nos reviewers qui pourront bénéficier, *via* notre nouveau site web (https://www.jfmo-dz.net/journal/index.php/medecine/), de ce système de récompense et de gratification. L'évaluation d'un article scientifique une fois enregistrée dans Reviewer Credits sera validée et certifiée, le reviewer disposera d'un index d'évaluateur bibliométrique, et pourra gagner des crédits.

Dans le même sillage, JFMO est indexé en 2021 à l'African Journal Online (AJOL) et au Directory Open Access Journal (DOAJ). L'AJOL, plateforme mondiale des revues scientifiques publiées en Afrique, englobe 591 journaux dont 306 Open Access Journals. Cette plateforme accroit l'accès en ligne au continent, améliore la qualité et promeut la relecture par les pairs. JFMO était le premier journal médical algérien à être indexé dans cette plateforme, à l'instar d'autres journaux algériens de technologie, d'informatique, d'économie et d'anthropologie.

Le DOAJ comprend 17 500 revues open access journals à comité de lecture, couvrant la technologie, la médecine, les sciences sociales, l'art et l'humanité.

Doucement, mais sûrement, notre journal continue d'implémenter les standards internationaux de l'écriture scientifique. Après son Indexation au catalogue de la célèbre National library of Medicine, JFMO est repéré et indexé dans l'index médicus de l'OMS, à l'instar de google scholar, researchgate et copernicus.

Le 7 avril 2024, un article publié dans JFMO (tuberculose cérébrale) est cité parmi les articles de la semaine de l'index médicus.

A ce jour, JFMO pèse 7 volumes, comprend 16 numéros, 127 articles publiés, un taux d'acceptation de 72%, et enregistre 24687 téléchargements dans la plateforme ASJP. Ce développement progressif du journal durant ces sept années a fait l'objet d'un documentaire de dix minutes présenté lors de cette manifestation scientifique.

Par ailleurs, les membres de la rédaction à travers le Professeur Abdelbaki BOUKERCHE ont rendu un vibrant hommage posthume à Feu le Professeur Merouane BOUKRISSA, en présence de ses enfants, pour avoir participé efficacement au développement du journal. En effet, Merouane BOUKRISSA est considéré comme un des membres fondateurs du journal et également un des concepteurs de la vitrine du journal (page de garde).Il a participé activement à l'édition de neuf numéros de JFMO. En outre, cinq membres de la rédaction du journal dont notre webmaster, ont été également récompensés pour leur participation active au développement et à la promotion du journal.

Les participants au 1er salon JFMO ont bénéficié d'une initiation à l'écriture scientifique par le biais de 5 conférences thématiques et 3 ateliers pratiques avec une forte participation. Ce premier salon JFMO a été un succès selon les participants que ce soit sur le plan organisationnel ou sur la qualité du programme scientifique et des conférenciers et animateurs d'ateliers. D'autres challenges doivent être relevés, notamment, l'indexation à Scopus, cela nécessitera beaucoup d'efforts dans l'amélioration de la qualité des articles scientifiques.

Abdelmadjid SNOUBER

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Journal de la Faculté de Médecine d'Oran

Article original

Evaluation of the performance of biochemical ratios and albumin's gradient in the etiological exploration of ascitic fluid

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KEY WORDS

Ascites, Exsudat, Transsudat, Light Criteria, Ratios biochimiques, Gradient albumine serum-ascite

Abstract

Biochemical exploration of effusion fluids plays a crucial role in the diagnosis of underlying pathologies. This study aimed to evaluate the performance of biochemical ratios and the albumin gradients in the diagnostic process of ascitic fluids.

Methods-The study was prospective, involving 56 samples from ascitic patients. For each patient, five biochemical parameters (glucose, protein, albumin, LDH, and total amylase) were performed in ascites and plasma samples. The ascites/plasma protein, LDH ratios, and serum-ascites albumin gradients (SAAG), were calculated to evaluate their diagnostic relevance.

Results - Twenty-eight adult patients presenting ascites were included in this study,18 women (64.28%) and 10 men (35.71%) with an M/F sex ratio of 0.55. The most efficient parameters to distinguish the transudate/exudate concept were: Ascitic proteins (p =0.01), ascitic/plasma proteins (p =0.004), ascitic LDH (p =0.011), ascitic/plasma LDH ratio (p =0.013), ascitic albumin (p = 0.012), ascitic albumin/plasma ratio (p = 0.002) and ascitic glucose/plasma ratio (p = 0.02). A threshold of 14 g/L of Albumine had a better positive predictive value than a threshold set at 20 g/L (73 vs 46%). The sensitivity, specificity, diagnostic efficiency,and positive and negative predictive values for SAAG were 100%, 64%, 78%, 64%, and 100% respectively, and for the modified Light's criteria 78%, 86%, 82%, 80%, and 82% which hadbetter diagnostic efficiency and specificity than the classic Light's criteria with the respective comparative value 82 vs 78% and 86 vs 57% but less sensitivity (78 vs 100%). The criteria H20-30, H25, and TAL had good diagnostic efficiency with 75%, 75%, and 78% respectively.

Conclusion -The integration of biochemical ratios and the albumin's gradient significantly improves the differential diagnosis of ascites. It is essential to promote the use of these parameters in clinical practice to improve the treatment of patients with ascites.

1. Introduction

The biochemical analysis of body fluids is essential for the diagnosis of medical conditions that lead to fluid effusion (1). Ascites is the accumulation of fluid in the peritoneal cavity caused by serious underlying diseases (2) and is among the most common effusions submitted to the medical laboratory. It is classified according to the underlying pathophysiological process, either as an exudate or a transudate, by the presence or absence of portal hypertension. Liver cirrhosis is the most common cause (75%) of ascites in adults in the Western world, followed by cancer (10%), heart failure (3%), tuberculosis (2%), and pancreatitis (1%). The establishment of an etiological diagnosis is necessary to guide treatment decisions(3). The biochemical analysis of ascitic fluid is commonly used for diagnostic orientation.

Usually, it is possible to distinguish the mechanism of ascite formation, meaning exudate from transudate, using the total protein concentration in ascitic fluid (TPasc), with a cut-off value of 25 g/L. However, this approach does not provide good diagnostic performance (diagnostic accuracy 56%) (4). To improve the diagnostic effectiveness, the criteria of Light et al. (LC) previously used for pleural effusion fluid, were adapted for ascites. An exudate is defined by the presence of 2 of the following criteria: a TPasc/TPserum ratio(TP ratio) > 0.5, an LDH level> 165 IU/l, or an LDH asc/LDH serum ratio (LDH ratio) > 0.6 (5).

In addition, the use of serum-ascites albumin gradient (SAAG) can differentiate ascites caused by portal hypertension (hepatic cause) from other non-hepatic causes, providing a better diagnostic approach. Indeed, an SAAG of 11g/l indicates cirrhotic ascites associated with portal hypertension, while an SAAG < 11g/l could be in favor of a non-hepatic cause: peritoneal carcinomatosis, peritoneal tuberculosis, pancreatic disease, or nephrotic syndrome(6).

These measurements proved to be more reliable than the quantification of biochemical markers only in ascitic fluid, allowing a better characterization of ascites and providing more importantinformation. The importance of biochemical analysis in the diagnostic approach of ascites still raises a scientific debate.

The objective of this study is to evaluate the performance of different biochemical ratios and SAAG in the diagnostic approach of ascites and to propose other diagnostic criteria.

2. Materials & Methods

This prospective study evaluated the biochemical ascites/plasma ratios and SAAG for the etiological diagnosis of ascites. The study was conducted in 12 weeks on hospitalized patients with ascites from February 12 to May 3, 2023. The inclusion criteria were: patients over 18 years old with clinically confirmed ascites and patients who gave informed consent to participate in the study. The criteria for non-inclusion were patients withcontraindications to ascitic tap (paracentesis), patients requiring ultrasound-guided paracentesis, patients with refractory or septated ascites that make sampling impossible, and patients with insufficient blood samples. The samples were collected in grey sodium fluoride tubes to inhibit glycolysis. The ascitic tap and blood sampling were performed at the same time to avoid any temporal differences in the sampling conditions. The macroscopic analysis of ascites was performed for each sample.

Biochemical analysis was performed on the RESPONS 920 DiaSys® analyzer after centrifugation of samples for 10 minutes at a speed of 2290 rotations per minute (RPM); the following parameters were measured: Glucose (Hk/G6PD FS Method), Protein (BIURET FS Method), Albumin (BCG FS Method), LDH (Lactate/Pyruvate IFCC FS Method) and Total Amylase (EPS-G7 IFCC FS Method).

We proposed five criteria for diagnosis improvement: modified light's criteria (LC'), H20-30 and H25criteria, TAL criteria, and finally the albumin cut-off value. LC' suggests that the presence of one positive criterion among LC, such as LDHasc > 165 IU/L, LDH ratio > 0.6, or TP ratio > 0.5, is enough to discriminate exudativeascites. The H20-30 criterion is based on two parameters: TP and LDH asc. A TP level below 20 g/l and an LDHasc above 165 IU/L would indicate an exudate. A TP greater than 30 g/l confirms the presence of an exudate, regardless of LDHasc level. However,if the TP concentration is between 20 and 30 g/l, only the LDH asc level would be considered for diagnosis (Table 1).

The third criterion proposed is H25, including the following criteria: if the TP is less than 25 g/l and the LDH asc is greater than 165 IU/L, the ascites is considered as an exudate. As far as, if the TP is greater than 25 g/l and the LDH asc is less than 165 IU/L. conversely if the TP is < 25 g/l with an LDH asc level<165 IU/L, or a TP greater than 25 g/l and an LDH asc > 165 IU/L. the ascites is a transudate. The fourth criterion is the Albumin cut-off valueof 14 g/l which classifies ascites,as exudate or transudate, but also according to the presence or absence of portal hypertension (PHT). A value below 14 g/l is in favor of transudative effusions and leads to the diagnosis of PHT, while a value above 14 g/l is in favor of exudative effusions and excludes PHT.

The TAL criteria are based only on the levels of TP, LDH, and Albumin in ascitic fluid (Albasc). The cut-off values were respectively: 25 g/l, 165 IU/l, and 14 g/l. If only one of these criteria is positive, the pathophysiological mechanism of ascite formation is exudative. The data was analyzed by the IBM® SPSS statistics version 21. The Student's t-test for independent samples and the ANOVA one-way test were used to compare the means.

The p-values less than 5% were considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic effectiveness were calculated as shown in Table 2.

Table 1. Differential diagnosis of ascites based on H20-30 criteria

H20 30	TP<20g/l		20 g/l >TP ≥ 30 g/l		TP ≥ 30 g/l	
	LDH <165 UI/ l	LDH >165 UI/ l	LDH <165 UI/ l	LDH >165 UI/ l	LDH <165UI/l	LDH >165UI/l
Clinical diagnosis	Transudate	Exsudate	Transudate	Exsudate	Exsudate	Exsudate
The positive criterion is taken into account	/	LDH	LDH	LDH	TP	/

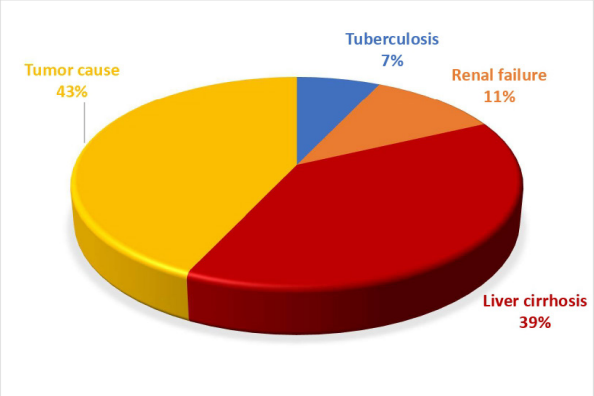
Table 2. Contingency table

	Reference test		
Test result	Presence of disease	Absence of disease	
Positive test	True positives (a)	False positives (b)	VPP = a/ (a + b)
Negative test	False positives (c)	True negatives (d)	VPN = d/(c + d)
	Sensitivity = a / (a +c)	Specificity =d / (b + d)	Total = N
Diagnostic effectiveness = (a + d) / N			

3. Results

Sixty samples were collected (30 ascites samples and 30 blood samples). However, two samples were excluded due to insufficient collection. A total of 28 patients with ascites were included in this study. There were 18 women (64.28%) and 10 men (35.71%) with an M/F sex ratio of 0.55. The average age of the patients was 57.5 ±15.69 years with extremes ranging from 21 to 86 years. The different causes of ascites are shown in figure 1.

Figure 1. Distribution of the sample according to etiology



Macroscopic analysis of the samples showed that the most common appearance is that of a citrine yellow liquid found in 82% of cases (23 patients). Three samples had an icteric appearance (11%). On the other hand, the least common appearance is that of a dark brown liquid, which was observed in only one patient (3.5%), as well as the haematic appearance (3.5%).

Seventeen patients had a SAAG ≥ 11g/l (60.71%) against 11 patients (39.29%) with a gradient < 11 g/l. According to protein rates, 18 samples were transudates and 10 exudates, however according to the light criteria 20 were transudates and 8 were exudates.

The analysis of the performance of the biochemical parameters showed that the ratios and the SAAG were the most significant in the distinction between an exudative and transudative process (**Table 3**).The tie-in calculation showed that the CLs accord in 86% with the TP, and in 100% with the LDH asc and the LDH's ratio.

Table 3. Expression of the parameters measured as average ± standard deviation depending on the transudate/ exudate's concept

	Transudate	Exsudate	
	Average ± standard deviation	Average ± standard deviation	P
TPasc	15.17 ± 8.41	26.04 ± 11.96	0.01 S
TPplasma	54.35 ±5.24	52.00 ± 7.91	0.36 NS
Ratio TP	0.28 ± 0.15	0.50 ± 0.20	0.004 S
LDHasc	66.08 ± 36.37	380.85 ± 395.78	0.011 S
LDHplasma	262.50 ± 94.31	408.21 ± 254.86	0.06 NS
Ratio LDH	0.30 ± 0.15	1.04 ± 0.96	0.013 S
Albasc	9.30 ± 5.64	16.10 ± 7.54	0.012 S
Albplasma	27.86 ± 4.61	26.48 ± 4.92	0.44 NS
Ratio Alb	0.32 ± 0.17	0.60 ± 0.24	0.002 S
SAAG	18.50 ± 5.18	10.37 ± 6.85	0.002 S
Glucoseasc	1.19 ± 0.59	1.14 ± 0.52	0.82 NS
Glucoseplasma	1.01 ± 0.42	1.19 ± 0.52	0.34 NS
Ratio Glucose	1.15 ± 0.11	0.97 ± 0.23	0.02 S
Amylaseasc	32.22 ± 16.19	38.69 ± 39.32	0.57 NS
Amylaseplasma	50.71 ± 24.79	43.35 ± 25.16	0.44 NS
Ratio Amylase	0.69 ± 0.31	0.78 0.41	0.51 NS

The tie-in calculation showed that the CLs accord in 86% with the TP, and in 100% with the LDHasc and the LDH's ratio. On the other hand, with the TP's ratio, the agreement was 75%. Table 4 summarizes the results of the evaluation of the threshold of distinction, specificity, sensitivity, PPV, NPV, and diagnostic effectiveness of the biochemical parameters and the criteria that we proposed according to the exudate/ transudate concept. Table 5summarizes the results of the evaluation of specificity/sensitivity, PPV/NPV, and the diagnostic effectiveness of SAAG, Albumin, and albumin ratio according to the presence or absence of PHT.

Discussion

In this study, we evaluate the relevance of some biochemical parameters, their ratios, and the Albumin gradient in the process diagnostic of ascites. results allowed us to propose diagnostic criteria that increase the performance of distinction between exudative and transudative liquids to guide the etiological diagnosis of ascites.

Our results were consistent with the majority of studies; female predominance was observed. These results are consistent with previous observations by Sidibé et al. 2009 (7) and Adhemar et al. 2016 (8) which reported proportions of 54.1% and 66% of women respectively. In a memory work carried out in the Médéa region in 2017 (9), the frequency found was also similar to ours (64%).

This predominance could be explained by the fact that women are more likely to develop ascites than men. Indeed, a study conducted in the United States in 2020 (10) showed that women had a significantly higher susceptibility than men for most chronic diseases other than cirrhosis, such as cancers (ovarian cancer, breast cancer). breast and cervix), diabetes, high blood pressure, congestive heart failure, and stroke. In our study, the most common etiology of ascites was cancers, followed by cirrhosis, contrary to the studies of Yousouf et al. 2017 (11), Sastry et al. 2017 (12), Sidibe et al (2009) (7), Chikyala 2023 (13) and Khan F.Y et al 2007 (14), where it represented the first etiology. This difference could be attributed to the limited number of patients included in our sampling.

The macroscopic appearance of samples revealed that the majority of cases presented a citrine color of ascitic fluid. Similar results were reported in the study of I. Chaouch and M. Ettahri in Médéa 2017 (9), and Yousouf et al. 2017 (11) revealed a rate of 80 %, while no chylous appearance was observed. In the literature, CL and SAAG (albumin-serum ascites gradient) are recognized as keys of the diagnostic strategy for the effusions classification into transudates and exudates. However, in current clinical practice, biochemical exploration of ascites focuses on the measure of parameters in ascites fluid but in this study, we included calculations of ratios and SSAG, then we classified the parameters in two categories: useful and useless for the discrimination between exudate and transudate. This approach highlighted the importance and usefulness of measuring TP and SAAG. Our results agree with those reported by Cabantous P 2021 (15) and we also found that measuring glucose in ascites was useless. Nevertheless, it is important to note that statistical significance was noted in the glucose ratio, suggesting that its assessment could be relevant to detect possible metabolic activity in ascites.

for amylase, contrary to the reference study we observed, that its dosage was useless. This difference could be attributed to the fact that we did not have ascites with pancreatic origin, which explains the lack of significant correlation. Similarly, Cabantous P et al (15) found that the LDH assay was useless, while our results showed that its assay was very useful. In addition, our results showed that the Albasc dosage and the calculation of the ratios: TP, Alb, LDH, and glucose were significant and useful to guide the diagnosis, except the amylase ratio which was not significant. The study of concordance of the different parameters with Light's criteria allowed us to note that the TP measurements are more in agreement with the CL than the TP ratio in the physiopathological classification.

diagnostic markers the most correlated with Light's criteria, in comparison with TP and its corresponding ratio.The results also revealed that the TP ratio is more reliable and precise for the classification of ascites into transudates and exudates. Indeed, the TP ratio presented better sensitivity/ specificity and better diagnostic efficiency than the ascites concentration of total proteins. This could be explained by analytical variability and systemic errors that can occur during the analysis. However, these variation factors are largely eliminated and switched by the calculation of the TP ratio. According to the study by Kahn AM et al. (16), LDH levels in transudate ascites are typically around 200 IU/L. Additionally, for clinical presentation of patients with exudative ascites primarily due to a malignant cause, LDH levels are greater than 250 IU.

Our observations are in agreement with these results, because we obtained an average of 66.08 ± 36.37 IU/L for transudate ascites, while the average for exudative ascites was 350.85 ± 395.78 IU. Furthermore, the application of this parameter and its ratio demonstrates a sensitivity of 100% and a specificity of 57%, with a diagnostic efficiency of 78%. We also observed a similarity in sensitivity and diagnostic efficiency between CL and SAAG, however, SAAG presents higher specificity compared to CL. Our results are consistent with the study conducted by BURGESS et al. (17), who compared the accuracy of CL, cholesterol level, cholesterol ratio, bilirubin level, and SAAG in distinguishing exudates from transudates in 393 patients. They found that CLs were the most accurate criteria (93%), with a sensitivity of 98% and a specificity of 83%.

The SAAG was the second-best performing test, with an accuracy of 89%, sensitivity of 87%, and specificity of 92%. Among the 19 transudates misclassified by CL in this study, 13 were correctly classified by SAAG. The results demonstrated that SAAG presents both better sensitivity and specificity compared to TPasc for the diagnosis. These findings are consistent with several previous studies (12,18,19).

Our study also showed that the diagnostic accuracy of SAAG is better than that of TP (78 vs 71%), which is in agreement with several studies: Runyon et al. (20) (USA) (96.7 vs 55.6%), Akriviadis et al. (21) (Greece) (98 vs 52%), Younas et al. (18) (Pakistan) (96 vs 56%),AL-knawye et al.(22) (Saudi Arabia) (94 vs 81%).Unlike previous studies, our study observed a lower PPV for SAAG compared to TPasc, with rates of 64% and 66% respectively. It is important to note that PTs can be influenced by other factors and are not specific to a single cause of ascites, which may confound the etiological diagnosis and result in false-positive results, thereby affecting sensitivity and specificity measurement & therefore The PPV of the TP asc. However, regarding NPV, SAAG showed superior performance compared to protein rates, with rates of 100% and 80% respectively. Our results are consistent with several previous studies (14, 18, 23).

The difference in accuracy between SAAG and TP in diagnosing ascites may be explained by the misclassification of ascites according to the transudate and exudate concepts based on total proteins. In our study, we found that 5 patients with malignant ascites were misclassified as transudates, as well as 1 patient with tuberculosis and 2 patients with renal failure who were misclassified as exudates. These classification errors may influence the diagnostic performance of PT compared to SAAG. In this study, we demonstrated that the TP measure in ascites alone is not sufficient to classify the physiopathological process in exudate/transudate, so it is recommended to replace it with SAAG which presents a better sensitivity, specificity, and diagnostic effectiveness. Or to use it in the second line. On the other hand, measurements of LDH and albumin in ascites provide a piece of important additional information to improve diagnostic accuracy. Additionally, the inclusion of biochemical ratios adds diagnostic value, with similar efficacy to SAAG, whichoffers better assessment and diagnostic guidance of ascites.

The ascites and blood samples are essential for calculating the different biochemical ratios and SAAG, but it is not always possible to do it for both at the same time. Thus, the introduction of other criteria can be necessary to evaluate the diagnosis. Indeed,we proposed CH20-30 and CH25 criteria that are mainly based on TPasc and LDHasc, while the TAL criteria take into account TPasc, Albasc, and LDHasc, and finally, Albasc with a threshold of 14 g/ L.

Our data showed that TAL criteria have the best performance in diagnostic efficiency, sensitivity, and precision. The CL', H20-30, and H25 criteria, for their part, have a better capacity to avoid false positives. Conversely, only the CL criteria offered the best liability, reliability, and precision to correctly identify true positives and true negatives samples.

These proposed criteria constitute an acceptable alternative to improve diagnostic performance when it is impossible to take both samples simultaneously. However, given the small number of our sample, which constitutes the main limitation of this study, it is desirable to validate these criteria through studies including a larger cohort to strengthen their reliability.

Conclusion

This study highlights the importance of a global and integrated approach to the biochemical exploration of ascites. We demonstrated that biochemical ratios and albumin gradients have an important role in understanding the physiopathological mechanism of ascites, and in making a precise clinical diagnosis. These measurements offer better performance than simple measures of biochemical markers in ascites and provide valuable information for diagnosis and patient management. Criteria that we proposed led to a significant improvement in diagnostic accuracy. Furthermore, the combination of LDHasc, Albasc, and TPasc offers an interesting alternative when taking ascites and blood samples simultaneously is difficult, also the LDH ratio offers a relevant alternative when other measures are not available. These different tests will contribute to better quality of care by providing precise information concerning the differential diagnosis of ascites; and by guiding appropriate therapeutic decisions to optimize the management of patients with ascites and improve their prognosis.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Article original

Prévalence et gestion des effets indésirables notifiés suite à l'utilisation de bévacizumab dans la prise en charge des cancéreux à l'EPH de Chlef

Prevalence of adverse effects reported by bevacizumab use and their management in cancer patients care at Chlef Public Hospital

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MOTS CLES

Effet indésirable, cancer, bévacizumab, antinéoplasique, pharmacovigilance

Résumé

Introduction-Les effets indésirables (EI) observés au cours des essais cliniques de bévacizumab ne sont pas applicables à la pratique clinique, car certains patients ne répondent pas à leurs critères d'inclusion. L'objectif de cette étude était de rapporter la prévalence des effets indésirables notifiés par l'utilisation du bévacizumab et leur gestion dans la prise en charge des cancéreux à l'Établissement Publique Hospitalier de Chlef.

Matériels et Méthodes-Il s'agissait d'une étude rétrospective du 01 mars au 31 mai 2022, portant sur les patients traités par le bévacizumab seul ou en association avec la chimiothérapie. Le critère de jugement principal est la prévalence des EI liés à l'utilisation des posologies normales ou d'un surdosage du bévacizumab. Les données sont collectées à partir des dossiers de patients et analysées par un logiciel.

Résultats-: Au total, 40 patients sont inclus dont 29 femmes, d'âge moyen de 55,87 ± 12,54 ans et 168 EI étaient déclarés, soit une moyenne de 4,20 EI par patient. Une prédominance des effets gastro-intestinaux (n=37) et l'hypertension (n=04) et la protéinurie (n=02) ont été les EI les plus graves. L'arrêt temporaire du bévacizumab était chez 22,50 % dont deux cas à cause d'une hypertension et deux cas à cause d'une protéinurie élevée. Quatre-vingt sept et demi pourcent recevaient un traitement palliatif aux EI ainsi qu'une surveillance de l'hypertension et de la protéinurie.

Conclusion-La prévalence des EI notifiés est élevée. Presque un quart des patients ont bénéficié d'un arrêt temporaire du bévacizumab dont quatre à cause de l'hypertension et de la protéinurie, ceci est nécessaire afin d'optimiser l'adhésion thérapeutique.

KEY WORDS

Adverse effect, cancer, bevacizumab, antineoplastic, pharmacovigilance

Abstract

Objective-Adverse effects (AEs) observed during clinical trials of bevacizumab are not applicable to clinical practice, as some patients do not meet their inclusion criteria. The objective of this study was to report the prevalence of adverse effects reported by bevacizumab and use their management in cancer patient's care at Chlef Public Hospital.

Materials & Methods-This was a retrospective study from March 1 to May 31, 2022 on patients treated with bevacizumab alone or in combination with chemotherapy. The primary endpoint was the prevalence of AEs related to the use of normal dosages or an overdose of bevacizumab. Data were collected from patient records and analyzed using software.

Results-40 patients were enrolled, including 29 women, with a mean age of 55.87 ± 12.54 years, and 168 AEs were declared, i.e. an average of 4.20 AEs per patient. A predominance of gastrointestinal effects (n=37) and hypertension (n=04) and proteinuria (n=02) were the most serious AEs. The temporary discontinuation of bevacizumab was in 22.50%, two cases of them because of hypertension and two cases because of high proteinuria. Eighty seven & half percent received palliative treatment for AEs as well as monitoring of hypertension and proteinuria.

Conclusion-The prevalence of reported AEs is high. Almost a quarter of the patients benefited from a temporary cessation of bevacizumab, four of them because of hypertension and proteinuria, this is necessary in order to optimize therapeutic adherence.

1.Introduction

Le bévacizumab est le premier anticorps monoclonal dirigé contre le facteur de croissance de l'endothélium vasculaire (VEGF) [1]. C'est un inhibiteur de l'angiogenèse, qui ralentit la croissance de nouveaux vaisseaux sanguins [1,2]. Il est indiqué dans le traitement du cancer colorectal, du poumon, du sein, du rein, de l'ovaire, le glioblastome et d'autres cancers. Contrairement à la chimiothérapie qui attaque les cellules cancéreuses, le bévacizumab bloque l'apport sanguin qui alimente la tumeur, ce qui empêche la tumeur de se développer [3,4]. De nombreux effets indésirables (EI) associés au bévacizumab ont été observés au cours des essais cliniques, y compris l'hypertension, tachycardie supra-ventriculaire, thrombose veineuse profonde et micro-angiopathie, dyspnée, perforation gastro-intestinale,syndrome d'érythro dyesthésie palmoplantaire, protéinurie, douleur pelvienne,asthénie,déficit en vitamine B12, larmoiement, etc [5-9]. Cependant, dans la plupart de ces essais, les patients ont été hautement sélectionnés avec des protocoles de traitement standardisés. Par conséquent, les données des essais cliniques ne sont pas pleinement applicables à la pratique clinique, car de nombreux patients dans le monde ne répondent pas aux critères d'inclusion des essais cliniques.

Quant à la gestion des EI, une question importante se pose, existe-il une stratégie d'éducation thérapeutique ?

L'objectif de cette étude était de rapporter la prévalence des EI notifiés et leur gestion, suite à l'utilisation de bévacizumab dans la prise en charge des cancéreux au service d'oncologie médicale de l'établissement publique hospitalier (EPH) de Chlef

2. Matériels et méthodes

2.1. Type de l'étude

Il s'agit d'une étude rétrospective réalisée sur une période de trois mois, allant du 01 mars au 31 mai 2022, portant sur les patients traités par le bévacizumab seul ou en association avec la chimiothérapie au service d'oncologie médicale de l'EPHde Chlef.

2.2. Population d'étude

Ont été inclus dans l'étude, les patients adultes de tous sexe ayant un cancer dont l'indication thérapeutique repose sur l'utilisation du bévacizumab : cancer du sein, de l'ovaire, cancer colorectal, cancer bronchique non épidermoïde et le cancer du col utérin.

Ont été exclus de l'étude, les patients présentant un manque d'informations essentielles.

2.3. Schéma d'étude

Le bévacizumab est utilisé à la dose de 5 mg/kg ou 10 mg/kg, toutes les deux semaines, ou à la dose de 7,5 mg/kg ou 15 mg/kg, toutes les trois semaines, seul ou en association avec la chimiothérapie, selon les protocoles suivant :

— Carboplatine AUC 5 + paclitaxel 175 mg/m2 + bévacizumab 15 mg/kg chaque trois semaines dans le cancer de l'ovaire ;

— Oxaliplatine 130 mg/m²+ capécitabine 1000 mg/m² +bévacizumab 10 mg/kg, toutes les deux semaines dans le cancer du col de l'utérus ;

— Paclitaxel 175 mg/m2 + bévacizumab 7,5 mg/kg pour chaque trois semaines dans le cancer de sein métastatique;

— Irinotécan 200 mg/m² + capécitabine1000 mg/m² +bévacizumab 7,5 mg/kg pour chaque trois semaines dans le cancer de sein métastatique ;

— 5FU 500 mg/m2+ acide folinique 400mg/m² + irinotécan180 mg/m²+ bévacizumab 7,5 mg/kg, chaque trois semaines dans le cancer colorectal métastatique ;

— Carboplatine AUC 5 + pémétrexed 500 mg/m²+ bévacizumab 7,5 mg/kg pour chaque trois semaines dans le cancer bronchique non épidermoïde.

2.4. Recueil de données

Le questionnaire comprenait les éléments suivants :

— Identification et informations générales;

— Type du cancer ;

— Molécule (s) associée (s) au bévacizumab et nombre de cycles ;

— EI survenus (à quelle dose, durée, type et grade) ;

— Traitement palliatif de l'EI survenu ;

— Arrêt du traitement, suite à un EI (type et grade, arrêt provisoire ou définitif, persistance ou non de l'EI après l'arrêt).

2.5.Critères de jugement principal et analyse statistique

Le critère de jugement principal était la prévalence des EI liés à l'utilisation des posologies normales ou d'un surdosage du bévacizumab.La saisie, l'analyse statistique des données et l'édition des résultats ont été réalisées.

3. Résultats

3.1. Caractéristiques de la population d'étude

Les principales caractéristiques de la population d'étude sont représentées dans le tableau 1. Quarante patients ont été inclus dans l'étude, une prédominance féminine (72,50 %) est constatée avec un sex ratio égal à 0,38. L'âge moyen des patients est de 55,87 ± 12,54 ans avec des extrêmes de 25 ans et 75 ans. Quatre tranches d'âge sont identifiées, les tranches d'âge les plus touchées par la pathologie sont celles de 51 à 64 ans et de 65 à 75 ans.

Seulement 07,50 % patients suivaient un régime sans sucre, 12,50 % patients étaient hypertendus, 07,50 % étaient diabétiques, 05,00 % souffraient d'une arthrose, 02,50 % souffraient d'une hypothyroïdie et 02,50 % s'étaient fait opérés pour une cholécystectomie.

Treize (32,50 %) patients étaient atteints d'un carcinome épithélial de l'ovaire, 25,00 % étaient atteints d'un cancer du sein métastatique, 25,00 % étaient atteints d'un cancer colorectal métastatique, 12,50 % atteints d'un cancer bronchique non à petites cellules et 05,00 % avaient un carcinome du col de l'utérus.

La majorité (72,50 %) des patients n'avaient aucun antécédent familial d'un cancer, par contre 10,00 % avaient des frères ou sœurs touchés, 07,50 % avaient des cousin(e)s touchés, 05,00 % leurs tante ou oncle, 02,50 % l'un de leurs parents et 02,50 % l'un de leurs grands-parents touchés par le cancer du poumon.

Quinze (37,50 %) patients ont reçu le bévacizumab en association avec « Carboplatine+paclitaxel », 15,00 % patients en association avec paclitaxel, 15,00 % seul, 05,00 % en association avec « Oxaliplatine + capécitabine », 05,00 % en association avec« Irinotécan +capécitabine », 05,00 % en association avec« Fluorouracile+ acide folinique + irinotécan » et les autres associations ont représenté 02,50 % pour chacune.

La majorité (47,50 %) des patients ont reçu le bévacizumab à la posologie de 7,5 mg/kg, une fois toutes les trois semaines, 25,00 % l'ont reçu à la posologie de 15 mg/kg toutes les trois semaines, 17,50 % à la posologie de 10 mg/kg toutes les deux semaines et 10,00 % à la posologie de 5 mg/kg toutes les deux semaines.

Tableau 1. Caractéristiques de la population d'étude

Caractéristique	Nombre (n=40)	Pourcentage (%)
Sexe		
Masculin	11	27,50
Féminin	2 9	72,50
Tranche d'âge (ans)		
25-35	03	07,50
35-45	05	12,50
45-55	05	12,50
55-65	14	35,00
65-75	13	32,50
Régime particulier		
Sans sucre	03	07,50
Aucun régime	37	92,50
Antécédent personnel		
Aucun	28	70,00
Hypertension	05	12,50
Diabète	03	07,50
Arthrose	02	05,00
Hypothyroïdie	01	02,50
Cholécystectomie	01	02,50
Type du cancer		
Carcinome épithélial de l'ovaire	13	32,50
Cancer du sein métastatique	10	25,00
Cancer colorectal métastatique	10	25,00
Cancer bronchique non à petites cellules	05	12,50
Carcinome du col de l'utérus	02	05,00
Antécédent familial d'un cancer		
Aucun	29	72,50
Frères ou sœurs	04	10,00
Cousin(e)s		
Tante ou oncle	03	07,50
Un des parents	02	05,00
Un des grands-parents	01	02,50
Molécule(s) associée(s) au bévacizumab	01	02,50
Aucune	06	15,00
Carboplatine + paclitaxel	15	37,50
Paclitaxel	06	15,00
Oxaliplatine + capécitabine	02	05,00
Irinotécan + capécitabine	02	05,00
Fluorouracile + acide folinique + irinotécan	02	05,00
Fluorouracile + acide folinique	01	02,50
Fluorouracile+ oxaliplatine+irinotécan	01	02,50
Carboplatine	01	02,50
Carboplatine+pémétrexed	01	02,50
Carboplatine+ docétaxel	01	02,50
Oxaliplatine	01	02,50
Paclitaxel+anastrozole	01	02,50
Posologie du bévacizumab		
7,5 mg/kg une fois toutes les 3 semaines	19	47,50
15 mg/kg une fois toutes les 3 semaines	10	25,00
10 mg/kg une fois toutes les 2 semaines	07	17,50
05 mg/kg une fois toutes les 2 semaines	04	10,00

3.2. Prévalence des effets indésirables notifiés

Les 40 patients avaient signalé au moins un EI. Au total,168 EI ont été déclarés, soit une moyenne de 4,20 EI par patient. Les femmes étaient plus sensibles aux EI que les hommes, elles présentaient 75,60 % des EI. La tranche d'âge la plus atteinte par les EI était celle de 65 à 75 ans, elle présentait 38,70 % des EI. La posologie 7,5 mg/kg toutes les trois semaines a induit le plus d'EI (50,60 %) suivi de la posologie 15 mg/kg toutes les trois semaines (26,80 %), tandis que la posologie 5 mg/kg toutes les deux semaines a induit le moins d'EI (04,76 %). La prévalence globale et celle des différents types d'EI notifiés sont résumés dans le Tableau 2.

Les EI les plus fréquents étaient les affections gastro-intestinales (n=37), suivies des troubles généraux (n=32) et des affections du système nerveux (n=28). Les EI fréquents étaient les troubles du métabolisme et de la nutrition (n=18), suivis des affections respiratoires thoraciques (n=15) et celle de la peau (n=08). Les EI les moins fréquents étaient les affections oculaires (n=04), affections vasculaires dont l'hypertension (n=04), affections du rein et des voies urinaires dont la protéinurie (n=02) et affections des organes de reproduction (n = 02).

3.3. Gestion des effets indésirables notifiés

La gestion des EI notifiés est présentée dans le tableau 3. Parmi les 40 patients sous Bévacizumab, 22,50 % patients ont arrêté temporairement le Bévacizumab dont deux patients l'ont arrêté à cause d'une hypertension artérielle dépassant les 150/100 mm Hg, deux patients à cause d'une augmentation de la protéinurie dépassant les 03 g/24 heures, deux patients à cause d'une altération de leur état général, un patient après avoir été touché par la COVID-19, un patient car il a souffert d'une forte asthénie et un patient l'a arrêté après avoir eu une perturbation de son bilan hépatique.

Cinq (12,50 %) patients n'ont reçu aucun traitement palliatif des EI. Pour pallier aux problèmes gastriques, 15 patients ont pris un anti-émétique l'ondansétron pour les nausées et les vomissements, huit patients ont pris un anticholinergique l'atropine pour la diarrhée, huit patients ont pris un corticoïde, le méthylprednisolone pour les douleurs, la fatigue et la perte d'appétit,deux patients ont été sous surveillance pour l'hypertension et deux patients ont été surveillés pour leur protéinurie.

Tableau 2. Nombre d'EI observés chez les 40 patients ayant présenté au moins un EI

Type d'effet indésirable	Nombre d'effets indésirables (n)
Nombre d'effets indésirables	168
Affections respiratoires thoraciques et médiastinales	15
Épistaxis	06
Rhinite	05
Toux	03
Dyspnée	01
Affections gastro-intestinales	37
Constipation	07
Diarrhée	07
Douleurs abdominales	07
Nausées	06
Stomatite	05
Vomissements	05
Affections de la peau et du tissu sous-cutané	08
Sécheresse cutanée	04
Dermatite exfoliante	02
Décoloration de la peau	01
Syndrome d'érythrodyesthésie palmoplantaire	01
Troubles du métabolisme et de la nutrition	18
Anorexie	10
Déshydratation	08
Affections du système nerveux	28
Céphalées	12
Dysgueusie	07
Neuropathie sensorielle périphérique	06
Dysarthrie	03
Affections oculaires	04
Larmoiement accru	03
Troubles oculaires	01
Affections vasculaires	04
Hypertension	04
Affections musculo-squelettiques et systémiques	18
Arthralgie	07
Faiblesse musculaire	05
Myalgie	04
Dorsalgie	02
Affections du rein et des voies urinaires	02
Protéinurie	02
Affections des organes de reproduction et du sein	02
Douleur pelvienne	02
Troubles généraux	32
Asthénie	11
Douleur	09
Fatigue	07
Perte de poids	05

Tableau 3. Gestion des effets indésirables notifiés

Type de gestion	Nombre de patients (n)
Absence d'arrêt du traitement par Bévacizumab	31
Arrêt du traitement par Bévacizumab	09
Arrêt Temporaire	09
Hypertension	02
Protéinurie > 3 g/24 heures	02
Altération de l'état générale	02
COVID-19	01
Asthénie forte	01
Perturbation du bilan hépatique	01
Traitement palliatif de l'EI	35
Anti-émétique : Ondansétron	15
Anticholinergique : Atropine	08
Corticoïde :Méthylprednisolone	08
Surveillance de l'hypertension	02
Surveillance de la protéinurie	02
Aucun traitement palliatif	05

Discussion

Dans cette étude, 40 patients ont été traités par bévacizumab, une prédominance féminine (72,50 %) a été constatée avec un sexe-ratio de 0,38. Ce qui est similaire à l'étude de Oza. AM et al. [17] sur le bévacizumab chez des patients atteints de tumeurs solides, une prédominance féminine était constatée avec un sexe-ratio de 0,56.

L'âge moyen des patients était de 55,87 ± 12,54 ans avec les tranches d'âge allant de 51 à 64 ans et de 65 à 75 ans les plus touchées par la pathologie. Ce qui est similaire à l'étude de Oza. AM et al. [17] dont l'âge moyen des patients était de 56 ± 0,9 ans.

L'hypertension artérielle était l'antécédent le plus fréquent (12,50 %) chez la population étudiée, ceci peut être confirmé par l'étude de Try. M et al. [15] sur les thérapies ciblées et l'hypertension artérielle où ils avaient constaté que 20 à 30 % des patients atteints de cancer peuvent être des hypertendus. Quant au diabète, notre constatation (07,50 %) partage la même hypothèse de l'étude de Gariani. K et al. [16] sur le diabète et cancer, une association pernicieuse où ils avaient démontré clairement la relation entre le diabète et le cancer en indiquant que le risque de survenue de ce dernier est augmenté chez les diabétiques.

La majorité (32,50 %) des patients étaient atteints du carcinome de l'ovaire suivis du cancer de sein (25,00 %) et du cancer colorectal (25,00 %).Ce qui est similaire à l'étude de Oza. AM et al. [17] sur le bévacizumab chez des patients atteints de tumeurs solides, parmi 95 patients cancéreux, 43,00 % étaient atteints du cancer de l'ovaire qui représentaient la majorité, suivi du cancer du sein (11,60 %) et cancer colorectal (07,37%).

L'analyse du statut héréditaire du cancer dans notre population a révélé que 27,50 % des patients ont des antécédents familiaux de la maladie. Ces résultats concordent avec ceux de l'enquête de Denis. B et al. [18], sur le dépistage et l'évaluation des facteurs néoplasiques familiaux, qui avaient constaté l'existence d'antécédents familiaux du cancer dans la moitié de dossiers étudiés. Ainsi, dans l'étude de Schoen. RE et al. [19], sur l'incidence et mortalité du cancer colorectal chez les personnes ayant des antécédents familiaux de cancer colorectal qui avait révélé que parmi 144 patients, 14 (10,30 %) décrivaient au moins un antécédent du cancer colorectal au premier degré, ceci est similaire à notre enquête étant donné que 12,50 % de la population étudiée avaient un antécédent au premier degré.

Seulement 15 % patients ont reçu le bévacizumab seul et la majorité (85 %) l'ont reçu en association avec une chimiothérapie dont l'association majoritaire a été« carboplatine + paclitaxel » 37,50 %, ceci répond aux recommandations de son RCP [10], ainsi dans l'étude de Evrard. J et al. [20], évaluant le protocole associant« bévacizumab + paclitaxel » dans le traitement du cancer du sein métastatique dont cette association était en 2ème rang (15 %).

La majorité (47,50 %) des patients ont reçu le bévacizumab à la posologie de 7,5 mg/kg, une fois toutes les trois semaines. Dans l'étude de Zhou. CH et al. [21], évaluant l'efficacité et la sécurité des différentes doses du bévacizumab associé au pémétrexed et au latine dans le traitement de première intention du cancer du poumon non à petites cellules avancé, où ils n'avaient pas détecté une différence significative d'efficacité et de sécurité entre le groupe recevant la posologie 7,5 mg/kg et le groupe recevant la posologie 15 mg/kg ,mais le rapport coût-efficacité du premier groupe était significativement meilleur que celui du deuxième groupe. Cela confirme en quelque sorte l'utilisation majoritaire de la posologie 7,5 mg/kg toutes les trois semaines dans notre étude.

Les 40 patients ont signalé au moins un EI et au total, 168 EI ont été déclarés, soit une moyenne de 4,20 EI par patient. Cette prévalence est élevée comme celle trouvée dans l'étude de Lee. SP et al.[22],sur la dose de bévacizumab affectant la gravité des EI dans les tumeurs malignes gynécologiques, ils rapportaient que parmi 154 patients, 121 (78,60 %) présentaient au moins un EI de tout grade. Les femmes ont été plus sensibles 75,60 % aux EI que les hommes, ce qui concorde avec l'étude de Haddaoui. C et al. [23], réalisée au centre anticancer de Sétif, évaluant le profil d'efficacité et de tolérance du bévacizumab chez les patients atteints du cancer de sein métastatique HER2 négatif.

Ainsi, dans l'étude de Zucchelli. G et al. [24] sur l'impact du sexe sur le profil d'innocuité de la chimiothérapie plus bévacizumab dans le cancer colorectal métastasique démontraient que les femmes atteintes présentaient un risque plus élevé que les hommes de développer des EI, en particulier les d'EI gastro-intestinaux, hématologiques, asthénie, nausées et vomissements.

La tranche d'âge la plus atteinte des EI a été celle âgée de 65 à 75 ans, elle a présenté 38,70 % EI. Ceci concorde avec les résultats de l'étude de Raman. AK et al. [25] sur les EI liés au bévacizumab chez divers groupes d'âge de patients âgés atteints d'un cancer colorectal avancé, ont constaté que l'incidence de la thrombose artérielle et de l'hypertension est accrue dans la population âgée.

La posologie 7,5 mg/kg toutes les trois semaines avait induit le plus d'EI (50,60 %). Ceci concorde avec les résultats de l'étude de Totzeck. M et al. [26] sur les EI cardiovasculaires chez les patients atteints de cancer traités par le bévacizumab dans une méta-analyse de plus de 20 000 patients qui a révélé que le traitement par bévacizumab augmente le risque d'EI en particulier l'ischémie cardiaque et cérébrale, d'EI veineux, de saignement et d'hypertension artérielle, et ce risque est encore important avec des doses élevées de bévacizumab. Cette diversité d'EI en terme de dose était également retrouvée dans notre étude étant donné la fréquence de survenue des affections vasculaires dont l'hypertension artérielle, des affections du rein et des voies urinaires dont la protéinurie était remarquablement augmenté chez les patients sous bévacizumab à la dose 10 mg/kg, ce qui rejoint la validité de la relation dose-effet.

Les EI les plus fréquents étaient les affections gastro-intestinales, les EI fréquents étaient les troubles du métabolisme et des affections respiratoires et les moins fréquents étaient les affections oculaires et vasculaire dont l'hypertension. Dans l'etude de Miles. D et al. [27] sur la prise en charge de la toxicité chez les patients recevant un traitement du bévacizumab, ils constataient que les événements fréquemment rapportés étaient l'hypertension (34 %), la protéinurie (38 %) et les hémorragies cutanéo-muqueuses (40 %) dont la plupart étaient de grade 1-2 de sévérité. Ces résultats concordent avec ceux de notre enquête particulièrement, en ce qui concerne l'hypertension (10 %), néanmoins, les résultats étaient différents quant à la protéinurie (05 %). Ainsi, l'étude de Senellart. H et al. [28] intitulée bévacizumab et hypertension artérielle ou protéinurie: prise en charge, ils ont démontré que l'hypertension était l'EI le plus fréquemment observé dans les essais cliniques et la survenue de la protéinurie était également fréquente chez les patients traités par bévacizumab.

Dans notre étude, les EI liés à l'association avec la chimiothérapie ont représenté la majorité des EI notifiés dont l'association « bévacizumab + carboplatine + paclitaxel » (25,00 %) induisit le plus d'EI, ceci correspond à l'étude comparative réalisée par Botrel. TEA et al. [29] dont l'objectif était d'évaluer l'efficacité et la tolérance du bévacizumab associé à la chimiothérapie par rapport à la chimiothérapie seule dans le cancer colorectal avancé ou métastatique, qui trouvaient que la survenue des EI était majoritaire chez les patients sous bévacizumab associé aux « carboplatine + paclitaxel ». Ainsi, dans la méta-analyse conçue par Shin. S et al. [30] qui avaient rapporté que l'association du bévacizumab à la chimiothérapie était associée à une augmentation significative du risque d'EI de haut niveau, notamment l'hypertension, la protéinurie, les hémorragies, la toxicité cardiaque et la fièvre neutropénique. Ces EI étaient également observés dans notre étude, notamment l'hypertension et la protéinurie, cependant, la toxicité cardiaque n'a pas été signalée. Les EI les plus graves dans notre étude étaient l'hypertension et la protéinurie, leur surveillance régulière avant chaque prise du bévacizumab était nécessaire.Brandes. AA et al. [31] avaient rapporté dans leur étude que chez les patients à faible risque, une pression cible inférieure à 140/90 mmHg peut être recommandée, tandis que chez les patients à haut risque, elle doit être abaissée à 130/80 mmHg.

Seulement un quart des patients ont arrêté temporairement le bévacizumab dont deux l'arrêtaient à cause d'une hypertension artérielle dépassant les 150/100 mmHg, deux l'ont arrêté à cause d'une augmentation de la protéinurie dépassant les 03 g/24 heures. Selon les données de la RCP du bévacizumab, l'hypertension artérielle dépassant les 150/100 mmHg et la protéinurie dépassant les 03 g/24 heures sont les EI les plus grave du bévacizumab. À cet effet, les oncologues du service d'oncologie médicale de l'EPH de Chlef ont recommandé d'interrompre temporairement le traitement par bévacizumab pour les deux patients ayant présenté une hypertension artérielle dépassant les 150/100 mmHg, jusqu'à la visite suivante. Quant à la protéinurie, l'administration du bévacizumab était retardée jusqu'au prochain rendez-vous pour les deux patients ayant présenté une protéinurie dépassant les 03 g/24 heures.

Dans l'étude britannique conçue par Plummer. C et al. [32] sur les recommandations d'experts sur la prise en charge de l'hypertension chez les patientes atteintes d'un cancer de l'ovaire et du col de l'utérus recevant du bévacizumab au Royaume-Uni, ils constataient que si la pression artérielle clinique est supérieure ou égale à 160/100 mmHg ou s'il y a eu une augmentation marquée de 20 mmHg pour la systolique ou de 10 mmHg pour la diastolique par rapport aux mesures précédentes, ils recommandaient de ne pas administrer la dose du bévacizumab et d'organiser une surveillance ambulatoire et à domicile de la pression artérielle. Si la pression artérielle moyenne est devenue inférieure ou égale à 150/95 mmHg, le bévacizumab peut être poursuivi lors de la prochaine visite clinique prévue.

Ceci est similaire à ce que nous avons trouvé dans notre étude où deux patients avaient arrêté leur traitement temporairement, après une augmentation de leur pression artérielle de 110/70 mmHg à 150/100 mmHg.

Dans l'étude faite par Benyounes. A et al. [33] sur la surveillance de la protéinurie chez les patients recevant du bévacizumab dans un centre anticancer communautaire à Philadelphie aux USA, ils rapportaient que l'intervalle de surveillance typique de la protéinurie était tous les deux cycles, le bévacizumab était interrompu à cause de la protéinurie élevée chez deux patients. Ceci est similaire aux résultats de notre étude.

L'ondansétron était utilisé pour pallier aux nausées et vomissements, l'atropine pour la diarrhée,le méthylprednisolone pour les douleurs, la fatigue et la perte d'appétit, deux patients étaient surveillés pour l'hypertension et deux patients surveillés pour leur protéinurie.

Dans l'étude de Dischl-Antonioni.I et al.[34], sur les diarrhées provoquées par les traitements systémiques anticancéreux, ils avaient rapporté que l'activité antiacétylcholinestérase de l'Irinotécan était responsable de diarrhées précoces durant les premières 24 heures, celles-ci peuvent être prévenues par l'atropine. Ce qui confirme l'utilisation de cette dernière dans notre étudepour pallier aux diarrhées. Il était souhaitable de faire cette étude sur des patients recevant uniquement le bévacizumab sans qu'il soit associé à une chimiothérapie, le nombre de patients n'étant pas suffisant (n=6) dans cet EPH.

Conclusion

L'étude a conclu que la prévalence des EI notifiés suite à l'utilisation de bévacizumab seul ou en association dans la prise en charge des cancéreux à l'EPH de Chlef était élevée. Les EI les plus graves étaientl'hypertension et la protéinurie dont l'arrêt du traitement était temporaire avec une surveillance jusqu'à normalisation.

L'arrêt temporaire du bévacizumab n'a été observé que chez neuf patients pour des EI sévères et irrémédiables, ce qui nous a conduit à suivre de façon rigoureuse les recommandations, quant à la gestion des EI.

La survenue de ces EI est donc inéluctable et ils apparaissent dès la mise en route du traitement, ce qui nous incite à contrôler de façon rapprochée les patients mis sous bévacizumab, les premiers mois de façon prophylactique ou curative (par exemple, conseiller au préalable un régime hyposodé, surveillance de la pression artérielle et surveillance de la protéinurie par le test de bandelettes urinaires) et de ne pas se précipiter à arrêter définitivement le traitement, car le plus souvent ils régressent au fil du temps afin de permettre une bonne adhérence thérapeutique et d'obtenir de meilleurs résultats.

Conflits d'intérêt

Les auteurs déclarent n'avoir aucun conflit d'intérêt.

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Article original

The impact of comorbidities and obesity on the severity of COVID-19 and risk factors for mortality: a prospective study in hospitalized patients

The impact of comorbidities and obesity on the severity of COVID-19 and risk factors for mortality: a prospective study in hospitalized patients

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KEY WORDS
Obesity; BMI; comorbidities; COVID-19; severity; mortality; risk factors

Abstract

Background- The studies of the clinical and demographic characteristics of COVID-19 patients around the world have made it possible to observe a rich semiology, which implicated obesity as a factor in the severity of COVID-19 pneumonia, and can lead to intensive care or even death. Some biomarkers have been identified as risk factors for mortality. The aim of this study was to verify obesity and the risk factors for mortality of COVID-19 infection.

Methods- This was a single-center prospective study carried out at Rouiba University Hospital, between March 19, 2020 to September 30, 2021. The clinical data were collected: age (year), BMI groups (≥ 30 and <30 kg / m2), sex, active smoking, medical history, clinical complaints, peripheral oxygen saturation (SpO2) at admission, and the length of hospital stay. A standard laboratory assessment and a chest CT without a contrast agent were performed. The prognostic was verified, and the healing, death, or transfers to intensive care were noted, and the data was analyzed.

Résultats-Our results showed an obesity rate (26.8%) and a mortality rate (5.3%) and found that obesity increases the risk of severity but not mortality in hospitalized patients. The risk factors for death from COVID-19 were the underlying chronic diseases including diabetes, COPD, renal failure and cardiovascular disease, hypoxia on admission, elevated serum LDH, CRP, and D-Dimer levels.

Conclusion-The inclusion of obesity and risk factors in therapeutic management strategies and prognostic scores will be essential to improve the prognosis of hospitalized COVID-19 patients.

1. Introduction

The SARS-CoV-2 coronavirus pneumonia outbreak was classified as a pandemic by the World Health Organization in March 2020 [1]. COVID-19 is causing extensive expressions ranging from mild upper respiratory tract symptoms to acute respiratory distress syndrome (ARDS), hypercoagulability, and cytokine storm [2]. However, the analysis of the clinical and demographic characteristics of COVID-19 patients around the world has made it possible to observe a rich semiology, which differs from one region to another and an estimated mortality rate of 3.2% [3].

Current literature suggests that complications from obesity potentially increase the severity of COVID-19, particularly in people under the age of 60 years [4]. Previous studies have shown the link between obesity as a potential aggravating factor in COVID-19 pneumonia [5] increased hospitalizations [6, 7], and the risk of invasive mechanical ventilation [8]. Various mechanisms may be involved, namely restrictive ventilatory deficit, lipotoxicity and induction of a pro-inflammatory state [9].

Other studies suggest that overweight and obese patients have a higher risk of serious illness during SARS-CoV-2 infection [10-13]. Overweight or obese patients require more frequent hospitalizations in intensive and semi-intensive care units, regardless of age. In addition, overweight and obese patients have a more frequent need for assisted ventilation due to SARS-CoV-2 pneumonia [8].

This assumes that obesity influences clinical manifestations and may contribute to disease progression and is considered potentially a prognostic factor of COVID-19 infection [14]. Algeria like the rest of the world is facing the spread of this pathology, and the first patient carrying this virus was detected on February 25, 2020. Obesity is reaching epidemic proportions in Algeria, and weighs heavily on the system of algerian health. In 2010, the TAHINA study reported a prevalence of total obesity in Algeria of 9.1% in men and 30.1% in women [15].

To effectively fight this epidemic, the algerian health authorities need to identify the risk factors for severe forms of patients hospitalized for COVID-19 [16]. Some authors have suggested that overweight and obese patients should be classified as high risk and should be minimally protected from infection and monitored more closely for SARS-CoV-2 pneumonia [10].

Symptoms of COVID-19 can include fever, cough, breathing difficulties, and organ failure. The severity of the disease can lead patients to intensive care or even death [17]. Old age, certain biomarkers such as LDH and D-Dimer have been identified as risk factors for mortality [18]. The aim of this study was to evaluate the association between obesity and the clinical, biological, CT, and prognosis profile of algerian patients hospitalized for COVID-19.

2. Pateints & methods

Study design

This study is the third part of a project analyzing clinical, biological and radiological data from algerian patients with COVID-19. The first part published, consists of a descriptive study , the second part concerned the analysis of the clinical, biological and radiological severity factors of algerian patients hospitalized for COVID-19: comparison between patients with normal and low pulsed oxygen saturation of hemoglobin (SpO2). As a large part of the methodology of this study was previously described [19, 20], only the main points of the methodology will be treated in this paper.

This was a single-center prospective study, which was carried out at Rouiba University Hospital, Algiers (Algeria) (period: March 19,2020 to september 30, 2021). Only patients with a positive diagnosis of COVID-19 [real-time PCR, antigen test [21-24] and pulmonary CT signs compatible with the infection were included in the study. Lack of BMI on admission was a non-inclusion criterion.

Data sources

The following clinical data were collected from a pre-established observation sheet and hospitalized patient records: age (year), BMI groups (≥ 30 and <30 kg / m2), sex, active smoking, notion of contact with a suspected / confirmed case of COVID-19, medical history, clinical complaints, peripheral oxygen saturation (SpO2) at admission, length of hospital stay.

Body weight was measured, height was self-reported, and indeed it was difficult to measure the height of the patients due to the clinical condition of the patients and to prevent any risk of SARSCoV-2 transmission.

Body mass index (BMI) was calculated using the usual formula (weight [kilograms] / height squared [square meters]) and categorized into five standard groups on the basis of National Heart Lung and Blood Institute criteria [25]: Insufficient BMI, <18.5 kg / m2; reference category, 18.5 kg / m2 at <25 kg / m2; overweight, 25 kg / m2 to <30 kg / m2; and obesity was defined as a BMI ≥30 kg / m2.

A standard laboratory assessment and a chest CT without a contrast agent were performed[19]. The prognostic was verified, and the healing, death, or transfers to intensive care were noted.

Statistical analysis

Quantitative and qualitative data were expressed as means ± standard deviations, and number (%), respectively. Missing data were removed from statistical analyzes [26]. Student's T-test and Pearson's Chi-square test were used to compare quantitative and qualitative data from the two groups, respectively. The results were entered using the statistica software (Statistica Kernel version 6; Stat Soft. France). A significance level <5% was retained.

3. Results

Among the 705 patients hospitalized and confirmed COVID-19, in the Department of pulmonology, 194 were excluded because anthropometric data was missing at admission. The 511 patients selected were divided into two groups: obese-group (137 patients) and non-obese group (374 patients).

Clinical profile and medical complaints

Table 1 exposes the characteristics and medical background of patients. Compared to the non-obese group, the obese-group included higher percentages of females (p<0.001), patients aged < 50 years (p=0.01), and the obese group was ~ 4-years younger (p=0.02). Included lower percentage of smokers (p=0.013), have higher percentage of hypertension (p=0.023) and have similar medical background.

Table 2 exposes the clinical complaints and physical exam' data of patients. The two groups have similar clinical complaints and similar physical exam' data (except for dyspnea: compared to the non-obese group, the obese-group included a higher percentage of patients with dyspnea, with anosmia and her with hemoptysis), and lower oxygen saturation level at admission.

Table 3 presents the biological (ESR and CRP) and hematological data of patients. The two groups had similar biological and hematological data and included similar percentage of patients having anemia, polycythemia, lymphopenia, basocythemia, hyperleukocytosis, thrombocytopenia, thrombocytosis, biological inflammatory syndrome, high CRP or ESR, but a lower level of leucopenia.

Table 4 presents the biochemical data of patients. Compared to the non-obese group, the obese-group have a higher value of LDH, a higher value of sodium, and to a lesser degree AST and creatinine.

Table 5 presents the CTs' data of patients, length of hospitalization and patients' issues.The two groups have radiological data without significant differences, except for the CT extension of more than 75% more marked in the obese group. The two groups have a similar duration of hospitalization also have an equal frequency of death and include identical percentages of patients transferred to intensive care.

Table 6 exposes the characteristics, and factors associated with in-hospital mortality. Compared to the survivor group, the non-survivor group had higher percentages of men (55.6% vs 47.7%), older ages (69.2 vs 55.4, p<0.0001) and more comorbidities; heart disease (37.0 vs 11.2, p<0.0001), hypertension (44.4 vs 32.4, p=0.197), diabetes (59.3 vs 24.0, p<0.0001), COPD (11.1 vs 1.2, p=0.0001), and chronic kidney disease (11.5 vs 1.5, p0.0003), but the same percentage of asthma (3.7 vs 5.6, p=0.678).

The non-survivor group included a higher frequency of dyspnea (84.6 vs 49.4, p=0.0008) and a lower level of saturation (72.8 vs 91.2, p<0.0001). Based on the biological profile, the non-survivor group included a higher level of polynuclear neutrophils (p=0.004), LDH (0.009), and C-reactive protein (p=0.017), and a higher number of patients with D-dimers greater than 1600 ng/ml (p=0.03) and a higher level of kaliemia(p=0.017). On the other hand, the same group included more patients with an extent of lesions between 50 and 75% (p=0.004), and greater than 75% (p=0.032).

Table 1. Characteristics and medical background of patients

		Total sample (n=511)	G1: BMI ≥ 30 kg/m^2 (n=137)	G2: BMI < 30 kg/m^2 n=374	p
Characteristics					
Sex (female)		265 (51.9)	87 (64)	178 (47)	<0.001**
Age ≥ 50 years		335 (65.6)	258 (57)	77 (69)	0.010**
Age (years)		56±15	53±14	57±16	0.002*
Height (m)		1.68±0.09	1.66±0.09	1.69±0.09	0.045*
Weight (kg)		79±15	93±13	74±11	<0.001*
BMI (kg/m2)		27.8±4.8	33.7±3.5	25.7±3.2	<0.001*
Corpulence Status	Underweight	11 (2)	-	11 (3)	-
	Normal weight	126 (25)	-	126 (34)	-
	Overweight	237 (46)	-	237 (63)	-
	Obesity level-1	101 (20)	101 (74)	-	-
	Obesity level-2	28 (5)	28 (21)	-	-
	Obesity level-3	8 (2)	8 (6)	-	-
Smokers		69 (14)	10 (8)	59 (16)	0.013*
Contact with a suspected/confirmed case of Covid-19		263(52)	71 (52)	192 (52)	0.530
Medical background					
Arterial hypertension		169 (33)	56 (41)	113 (30)	0.023*
Mellitus diabetes		132 (26)	35 (26)	97 (26)	0.929
Chronic respiratory disease and allergy		56 (11)	12 (9)	44 (12)	0.348
COPD		9 (2)	1 (1)	8 (2)	0.284
Asthma		28 (5)	8 (6)	20 (5)	0.829
Heart diseases		64 (13)	17 (12)	47 (13)	0.962
Thyroid diseases		46 (9)	17 (13)	29 (8)	0.093
Cancer		14 (3)	2 (1)	12 (3)	0.292

G: group. BMI: body mass index. Quantitative and categorical data were expressed as mean±standard deviation and number (%), respectively.
P (probability): p< 0.05 (*Student Test, **Two sided Chi-2): G1 vs. G2.

Table 2. Clinical complaints and physical exam' data of patients

	Total sample (n=511)	G1: BMI ≥ 30 kg/m^2 (n=137)	G2: BMI < 30 kg/m^2 n=374	p
Clinical complaints				
Fever	398 (78)	114 (83)	284 (77)	0.344
Cough	385 (75)	107 (79)	278 (74)	0.293
Dyspnea	261 (51)	84 (62)	177 (47)	0.004*
Hemoptysis	14 (3)	7 (5)	7 (2)	0.046*
Sore throat	132 (26)	36 (26)	96 (26)	0.867
Ageusia	190 (37)	59 (43)	131 (35)	0.071
Anosmia	176 (35)	60 (44)	116 (31)	0.007*
Abdominal pain	94 (18)	32 (23)	62 (16)	0.071
Vomiting and / or nausea	119 (23)	36 (26)	83 (22)	0.306
Diarrhea	195 (38)	61 (45)	134 (36)	0.060
Myalgia	303 (59)	90 (66)	213 (57)	0.056
Headache	283 (55)	83 (61)	200 (53)	0.122
Skin lesion	19 (4)	3 (2)	16 (4)	0.280
Asthenia	413 (81)	114 (84)	299 (80)	0.294
Anorexia	300 (59)	89 (65)	211 (56)	0.062
Chest pain	142 (28)	39 (29)	103 (27)	0.752
Eye burn	35 (7)	10 (7)	25 (7)	0.770
Fear of heights	117 (23)	33 (24)	84 (22)	0.629
Rhinorrhea	27 (5)	11 (8)	16 (4)	0.084
Physical exam' data				
Temperature at admission	37.3±0.9	37.4±0.9	37.2±0.9	0.318
Respiratory rate (cpm)	24±8	25±10	23±7	0.051
Heart rate (cpm)	90±16	91±15	89±16	0.176
Oxy-sat (%) at admission	90±10	88±11	91±9	0.004*
Fever (temperature ≥ 37,5°C)	117 (39.4%)	38 (46.91%)	79 (36.57%)	0.105
Tachypnea (respiratory rate > 20 cpm)	210 (60)	60 (69)	150 (57)	0.045*
Tachycardia (heart rate ≥100)	84 (18)	24 (21)	60 (17)	0.419
Bradycardia (heart rate ≤ 60)	8 (2)	1 (1)	7 (2)	0.408
Low oxy-sat (< 92%) at admission	315 (62)	69 (50)	246 (66)	0.002*

G: group. BMI: body mass index. Quantitative and categorical data were expressed as mean±standard deviation and number (%), respectively.
P (probability): p< 0.05 (*Student Test, **Two sided Chi-2): G1 vs. G2.

Table 3. Hematological, ESR and CRP data of patients					
		Total sample (n=511)	G1: BMI ≥ 30 kg/m^2 (n=136)	G2: BMI < 30 kg/m^2 n=375	p
Quantitative data					
Hemoglobin (g/dl)		12.9±1.7	12.8±1.6	12.9±1.8	0.601
Leukocytes (103/mm3)		7995±3931	7910±3429	8026±4102	0.779
Leucocyte count	NPN (103/mm3)	5961±3603	5781±3158	6009±3744	0.627
	EPN (103/mm3)	41±78	30±57	45±84	0.084
	BPN (103/mm3)	131±130	139±137	138±131	0.416
	Lymphocytes (103/mm3)	1184±728	1228±751	1168±743	0.430
	Monocytes (103/mm3)	666±541	688±648	657±514	0.606
Platelets (103/mm3)		262±104	266±118	261±101	0.660
ESR (1st h) (mm)		65±37	68±39	64±37	0.386
CRP (mg/L)		55±59	57±59	53±59	0.656
Patients' profile					
Anemia		154 (35)	36 (31)	118 (37)	0.255
Polycythemia		4 (1)	0 (0)	4 (1)	0.227
Leukopenia		44 (10)	6 (5)	38 (12)	0.040*
Lymphopenia		204 (47)	51 (44)	153 (48)	0.435
Basocythemia		128 (30)	38 (34)	90 (29)	0.335
Hyperleukocytosis		103 (23)	28 (24)	75 (23)	0.886
Thrombocytopenia		50 (11)	13 (11)	37 (12)	0.898
Thrombocytosis		26 (6)	9 (7)	17 (5)	0.352
High CRP		248 (63)	66 (63)	182 (63)	0.932
High ESR (1st h)		263 (82)	66 (81)	197 (82)	0.836
Biological inflammatory syndrome		358 (83)	92 (80)	266 (84)	0.377

BPN: basophilic polynuclear. BMI: body mass index. CRP: C-reactive protein. EPN: eosinophilic polynuclear. ESR: erythrocyte sedimentation rate. G: group. NPN: neutrophilic polynuclear. Quantitative and categorical data were expressed as mean±standard deviation and number (%), respectively.
P (probability): p< 0.05 (*Student Test, **Two sided Chi-2): G1 vs. G2.

Table 4. Biochemical data of patients					
		Total sample (n=511)	G1: BMI ≥ 30 kg/m^2 (n=137)	G2: BMI < 30 kg/m^2 n=374	p
Quantitative data					
Kidney function	Urea (g/L)	0.43±0.31	0.45±0.37	0.42±0.28	0.301
	Creatinine (mg/L)	11.81±10.28	13.27±16.16	11.29±7.07	0.072
Liver function	ASAT (UI/L)	44.80±30.99	49.39±34.54	43.06±29.54	0.039
	ALAT (UI/L)	40.86±39.31	43.08±35.68	40.80±41.52	0.601
	ALP (UI/L)	168.19±60.06	161.67±51.11	171.02±61.14	0.156
Serum electrolytes	Potassium (mmol/l)	3.90±0.48	3.82±0.53	3.92±0.46	0.063
	Sodium (mmol/l)	136.83±4.67	137.70±4.38	136.53±4.73	0.032*
Prothrombin level (%)		84.73±15.41	86.82±15.43	84.54±14.27	0.221
CPK (UI/L)		164.78±317.53	205.56±333.20	142.71±323.20	0.753
LDH (UI/L)		555.42±305.72	647.61±371.44	527.05±277.06	0.001*

ALAT: alanine amino-transferase. ALP: alkaline phosphatase. ASAT: aspartate amino-transferase. BMI: body mass index. CPK: creatine phosphokinase. G: group. LDH: lactico-dehydrogenase. Quantitative and categorical data were expressed as mean±standard deviation and number (%), respectively.
P (probability): p< 0.05 (*Student Test, **Two sided Chi-2): G1 vs. G2.

Table 5. Computed tomography scan data of patients, length of hospitalization, issues of patients				
	Total sample (n=511)	G1: BMI ≥ 30 kg/m^2 (n=137)	G2: BMI < 30 kg/m^2 n=374	p
Radiological signs				
ground-glass	455 (94)	128 (98)	327 (93)	0. 078
nodular ground-glass	239 (50)	72 (55)	167 (48)	0.158
diffuse ground-glass opacity	334 (69)	89 (68)	245 (70)	0. 778
crazy paving	169 (35)	44 (34)	125 (36)	0. 664
condensation	258 (54)	71 (54)	187 (53)	0. 860
CT extension of lésions				
<10%	106 (22)	25 (19)	81 (23)	0.327
10-25%	87 (18)	23 (17)	64 (18)	0.834
25-50%	138 (28)	36 (27)	102 (29)	0.683
50-75%	83 (17)	28 (21)	55 (15)	0.153
>75%	11 (2)	8(6)	3 (1)	<0.001
Length of hospitalization, issues of patients				
Hospital stay (day)	10.1±6.5	10.0±6.6	10.4± 6.2	0.605
Transfer to an intensive care-unit	49 (9.6)	16 (11.7)	33 (8.8)	0.332
Death	27 (5.3)	20 (5.3)	7 (5.1)	0.915

BMI: body mass index. G: group. Data were expressed as number (%). p (probability): p< 0.05 (* Two sided Chi-2): G1 vs. G2.

Table 6. Factors associated with in-hospital mortality				
Parameters at admission	Overall (N=511)	Survivors (N = 484)	Non-survivors (N = 27)	p
BMI, mean ± SD, kg/m2	27.83±4.82	27.85± 4.74	27.34 ± 6.11	0.589
Age years	56.2± 15.5	55.4 ±15.2	69.2 ±14.8	<0.0001*
Sex (male)	48.1(246)	47.7 (231)	55.6(15)	0.429
Smokers	13.9 (69)	13.4 (63)	23.1 (6)	0.166
Comorbidities				
Heart disease	12.5 (64)	11.2 (54)	37.0 (10)	<0.0001*
Hypertension	33.1 (169)	32.4 (157)	44.4 (12)	0.197
Diabetes mellitus	25.8 (132)	24.0 (116)	59.3 (16)	<0.0001*
Asthma	5.5 (28)	5.6 (27)	3.7(1)	0.678
COPD	1.8 (9)	1.2 (6)	11.1(3)	0.0001*
Chronic kidney disease	2 (10)	1.5 (7)	11.5 (3)	0.0003*
Symptoms				
Cough	75.5 (385)	75.0 (363)	84.6 (22)	0.268
Dyspnea	51.2 (261)	49.4 (239)	84.6 (22)	0.0008*
SpO2 >92%	61.8 (315)	64.3 (311)	15.4(4)	<0.0001*
Air ambient Oxy-sat (%)	90.3 ±9.6	91.2 ± 8.01	72.8± 17.1	<0.0001
Hemoglobin (g/l)	12.86± 1.75	12.9 ±1.7	12.4 ± 2.1	0.162
Polynuclear neutrophils (/mm3)	5961± 3603	5845 ±3557	7898 ±3879	0.004*
Lymphocytes (/mm3)	1184 ±729	1187 ±724	1134 ±816	0.719
ESR (1st hour) (mm)	65.3 ±37.6	65.2± 37.9	67.0 ±31.2	0.850
C-reactive protein (mg/l)	54.5 ±59.0	52.9 ±57.8	82.5± 72.1	0.017*
LDH level (u/l)	555.4 ±305.7	547.0 ±294.4	738.4 ±466.3	0.009*
D-dimers >1600 ng/ml	25.7 (75)	24.0 (64)	44.0 (11)	0.03*
Kaliemia (mmol/l)	3.90± 0.47	3.87 ±0.46	4.15± 0.70	0.017*
Natremia (mmol/l)	136.8 ± 4.67	136.7± 4.64	138.6 ±5.01	0.092
CT extent of COVID-19				
<10%	21.6 (106)	22.3 (104)	8.7 (2)	0.147
10-25%	17.8 (87)	18.2 (85)	8.7 (2)	0.245
25-50%	28.2 (138)	28.1 (131)	30.4 (7)	0.904
50-75%	16.9 (83)	15.8 (74)	39.1 (9)	0.004*
>75%	2.2 (11)	1.9 (9)	8.7 (2)	0.032*
Length of stay in the hospital (day)	10.1 ±6.5	10.0±6.2	11.1±9.9	0.332
Quantitative and categorical data were expressed as mean±standard deviation and number (%), respectively. p (probability) : p< 0.05 (*Student Test)				

Discussion

A few studies were available in the North African environment to assess the risk factors of dying during hospitalizations of patients with COVID-19. Our results could give a model to evaluate risk and use it at convenience in acute care settings.

In this study, we collected data from 511 cases of COVID-19. The cohort was a random group of patients representing the real situation of patients hospitalized in our department with 26.8% of obese patients, although obesity represents according to the Tahina study [15] 21.24% of the algerian population. In a large New York study of patients hospitalized for COVID-19, 41.7% had a body mass index (BMI)> 30 kg / m^2 and 19.0% a BMI> 35 kg / m^2[27]. Analysis of the data by BMI identified 2 groups with an average BMI of (33.7 vs 25.7) in the whole sample, and of (33.8 vs 25.8) in subjects less than 50 years old. In our study, the obese vs. non-obese group had higher percentages of women and patients under the age of 50 y. Comparable results were found in an Italian study, where the relationship between obesity and COVID-19 does not appear evident in the general population, on the other hand it was particularly clear in the youngest subjects [28].

In our study of patients under 50 infected with COVID-19, BMI was similar to the mean BMI of the entire sample, while in other studies in patients of under 50 years infected with SARS-CoV-2, the average BMI was higher, and this index seemed to decrease with age in COVID-19 patients [29-31]. The results suggest that obesity may be more prominent in young patients with COVID-19.

The comorbidities in the high BMI group were particularly less pronounced in the cohort of patients under 50 years, with fewer underlying illnesses such as hypertension, metabolic disease, diabetes and dysthyroidism, contrary to some studies already reported [6, 9, 32, 33].

The literature data precise that the effect of obesity on COVID-19 was independent of comorbidities, such as hypertension, and diabetes. This suggests an important pathophysiological link between a high level of adiposity and a poor prognosis of COVID-19 disease [11, 29, 34], according to Gao et al. [35], obesity has tripled the risk of worsening COVID-19. Obesity induces T cell depletion through constant low-grade inflammation, which alters the immune response and reduces its ability to confront the virus from the host [35, 36]. obesity may also interfere with the activation of immune cells [37]. Deng et al [38], have suggested in young patients, that visceral, hepatic, epicardial, and perirenal adiposity may predict the COVID-19 severity.

On analysis of chest imaging, we found that the distribution of lung lesions was slightly different between obese and non-obese patients. The cases of obesity also manifested a higher proportion of specific opacity in ground glass (98% against 93%). Lung damage involvement was slightly more extensive in obese patients, this difference becomes more pronounced, especially for CT lesions greater than 50%. Similar results have been described in the literature [14, 39].

On analysis of chest imaging, we found that the distribution of lung lesions was slightly different between obese and non-obese patients. The cases of obesity also manifested a higher proportion of specific opacity in ground glass (98% against 93%). Lung damage involvement was slightly more extensive in obese patients, this difference becomes more pronounced, especially for CT lesions greater than 50%. Similar results have been described in the literature [14, 39]. Indeed, obesity is the result of abnormal energy metabolism, which in turn lead to stress and tissue dysfunction [40, 41]. In our study, obese patients showed a slightly high rate of CRP and erythrocytic sedimentation levels than those who were not obese table 3, these markers of inflammation influence the progression and poor prognosis of COVID-19 disease.

Obesity provides a chronic environment for disease pathogenesis and is characterized by a low-inflammatory condition, which can lead to the production of depleted immune cells, and the body becomes more vulnerable to infections [8, 42, 43]. The excessive immune response to SARS-CoV-2 is the main reason for the severe forms of illness and the mortality of patients. The CRP was slightly higher in obese COVID-19 patients compared to non-obese patients in previous studies [44, 45]. In addition, significantly higher levels of LDH and hypernatremia in obese patients are associated with a slight, less pronounced elevation of transaminases mainly AST and hypokalaemia Table 4. BMI, ALAT and ASAT were independently and inversely associated with being discharged from hospital in time for these patients. One study found that obesity and abnormal liver function predispose patients with COVID-19 to prolonged hospitalization [46], in our study we found the same trend with more patients staying longer than 10 days among obese subjects and subjects with a high ALT level.

In our study, kalaemia was slightly greater in the group of obese patients (3.82 vs 3.92); sodium disorder, particularly hyponatremia, is a common occurrence in hospitalized patients with COVID-19 in a Chinese study, and is associated with a higher risk of serious illness and increased hospital mortality [47]. However, in our study, we found an association between hypernatremia, hospitalization duration, and mortality, table 6.

Indeed, the high prevalence of hypokalemia in patients with COVID-19 in Mediterranean studies suggests the presence of a disruption in the activity of the renin-angiotensin system due to severe infection of SARS-CoV-2 [48]. Additionally, this sensitive biomarker may reflect the progression of COVID-19. Hypokalaemia has been shown to be independently associated with the need for invasive mechanical ventilation [49]. Obesity can disrupt immune responses, making obese patients susceptible to infections, both bacterial and viral [50]. This increased risk had already been described for infections with the influenza virus,[50] with a longer duration of contagiousness in obese people compared to that in non-obese [49].

In our study, the mean hospital stay was similar to 10 days vs. 10.4 days, in fact, the hospital stay was the same in previous studies [33]. In our work, obese patients had lower oxygen saturation on admission (88% vs 91%).

We found no higher mortality or transfer rate to the intensive care unit for obese patients compared to those who were not obese in our sample (5,3 vs 5,1) for mortality, (11,7 vs 8,8) for transfer to the intensive care units. Identical results with a BMI were not found to be an independent predictor of mortality [51]. However in previous viral pandemics, it has been shown that obesity, especially severe obesity (BMI> 40 kg / m2), is associated with an increased risk of hospitalization, admission to intensive care and death [52, 53].

A systematic review and meta-analysis of 22 studies showed that obesity was associated with a poor prognosis for SARS-CoV-2 infection, marked by more cases of severe COVID-19, admission to intensive care, recourse to mechanical ventilation and rapid progression of the disease, especially in younger subjects (OR 3.30 vs 1.72). However, this meta-analysis did not find an association between obesity and hospital mortality [29].

Current literature suggests an association between obesity and increased mortality in patients with COVID-19 pneumonia in the general population, particularly in younger patients [10, 13]. However, a lower BMI ≤ 25 was associated with a decrease in the need for mechanical ventilation [13]. Obesity was significantly associated with a greater likelihood of death, and a higher percentage of death (32.61%) was noted in obesity classes II and III (BMI ≥35 Kg/m2)[63]. Group class I (BMI 18.5–24.9 Kg/m2) had the lowest percentage of death [54]. Group classI (BMI 18.5–24.9 Kg/m2) had the least percentage of meeting the primary endpoint [54]. Severe obesity is a relevant risk factor for COVID-19 severity and hospitalization in young adults, similar to that of aging patients [55]. Higher BMI in early adulthood was associated with severe COVID-19 many years later with a risk increase starting already at BMI ≥22.5 [56].

Studies show that having a BMI ≥ 30 kg/m2 is a significant risk factor in COVID-19 morbidity and mortality [57].

Comparing the survivor group with the non-survivor group in Table 6, the latter had higher percentages of males, older ages, and more comorbidities (heart disease, hypertension, diabetes, COPD, and chronic kidney disease, but the same percentage of asthma), the results were found by Kyoung Min Kim [58]. The non-survivor group had a higher frequency of dyspnea and a lower level of oxygen saturation. Based on the biological profile, the non-survivor group included a higher level of neutrophil polynuclear, LDH, and C-reactive protein, and a higher number of patients with D-dimer greater than 1600 ng/ml, which indicated that D-dimer could be an early marker to improve the management of COVID-19 patients[59]. In fact, hospital mortality was significantly higher in patients with high neutrophil count, lower lymphocyte count, elevated CRP, and D-dimer ≥ 2.0 µg/ml than those who had D-dimer < 2.0 µg/ml on admission [60]. On the other hand, the same group included more patients with an CT extent of lesions greater than 50%. The risk of mortality for COVID-19 patients could be evaluated using a lung CT-scan extent cut off [61].

Strengths and limitations

The strength of this study is prospective study included a single center with the same team of investigators, over 18 months, in a pulmonology Department. There were some limitations to the current study. First, our study cannot be considered exhaustive, and might be possible other factors that affect COVID-19 mortality, is the retrieval of clinical data was difficult for severely ill patients.

In summary, obesity contributes to clinical manifestations and can influence the progression and prognosis of COVID-19, with an accumulated risk of serious complications for obese subjects. Our cohort showed an obesity rate (26.8%) and a mortality rate (5.3%), and warned that obesity increases the risk of severity but not mortality in hospitalized patients for COVID-19. Therefore, the inclusion of obesity in prognostic scores and therapeutic management strategy will be essential to improve the prognosis of hospitalized patients with COVID-19. Risk factors for death from COVID-19 were a history of underlying chronic diseases including diabetes, COPD, renal failure and cardiovascular disease, hypoxia on admission, elevated serum LDH, CRP and D.Dimer linked to the survival status of COVID-19 patients.

Further studies are needed to assess the association between age, obesity, fragility, and clinical outcome in adults with COVID-19 disease.

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UPDATE

Pharmacogenomics : tailoring drug therapy to individual patients

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KEY WORDS

Pharmacogenomics, Personalized medicine, Drug response, Genetic variations, Clinical applications

Abstract

Pharmacogenomics, the study of how individual genetic variations influence drug response, holds tremendous potential for personalized medicine. This comprehensive literature review explores the current landscape of pharmacogenomics, focusing on its role in tailoring drug therapy to individual patients.

The introduction provides an overview of pharmacogenomics, its definition, and historical development. The subsequent sections delve into key subtopics, including the influence of pharmacogenomic variants on drug metabolism, the identification of genetic biomarkers for drug efficacy and safety, pharmacogenomic testing approaches, and clinical applications in various healthcare settings.

Ethical, legal, and social implications (ELSI) surrounding pharmacogenomics are discussed, along with future directions and challenges in this field. Through a meticulous analysis of existing research articles, clinical guidelines, and reviews, this literature review highlights the significance of pharmacogenomics in optimizing drug therapy, improving patient outcomes, and fostering the era of precision medicine.

Introduction and the text

Pharmacogenomics is an emerging field of study that investigates the influence of individual genetic variations on drug response. It encompasses the interdisciplinary approach of pharmacology and genomics to optimize drug therapy for individual patients [1]. Understanding the genetic basis of drug response is of paramount importance as it enables the tailoring of treatments to maximize efficacy and minimize adverse reactions [2].

The scope of pharmacogenomics extends beyond the identification of single gene-drug interactions. It involves the study of genetic variations that influence drug metabolism, drug target interactions, and drug transport mechanisms [3]. By uncovering the genetic factors responsible for interindividual variability in drug response, pharmacogenomics facilitates the development of personalized medicine approaches [4]. The significance of individual genetic variations in drug response cannot be overstated. Genetic polymorphisms in drug-metabolizing enzymes, such as the cytochrome P450 (CYP) superfamily, can lead to altered drug metabolism rates and subsequent variations in drug efficacy and toxicity [5]. Additionally, genetic variations in drug targets and transporters can affect drug binding affinity and distribution, thereby influencing therapeutic outcomes [6].

The historical background of pharmacogenomics traces back several decades. The field gained momentum in the mid-20th century with the discovery of inherited traits affecting drug metabolism, exemplified by the classic work on the inherited deficiency of glucose-6-phosphate dehydrogenase and its impact on primaquine-induced hemolysis [7]. The advent of molecular genetics and the Human Genome Project further accelerated progress in pharmacogenomics, enabling the identification of genetic variants associated with drug response [8]. In recent years, advancements in high-throughput genotyping technologies and cost-effective sequencing methods have enhanced our ability to identify genetic variations relevant to drug response. These technological breakthroughs, coupled with the increasing availability of large-scale genomic databases, have paved the way for the translation of pharmacogenomics into clinical practice [9].

II. Pharmacogenomic variants and drug metabolism

Drug metabolism, a critical process in determining drug response, is influenced by genetic variants in key drug-metabolizing enzymes, particularly the cytochrome P450 (CYP) superfamily. Cytochrome P450 enzymes play a vital role in the biotransformation of a wide range of medications, including many commonly prescribed drugs [5]. Genetic polymorphisms in CYP enzymes can lead to variations in drug metabolism rates, resulting in interindividual differences in drug efficacy, toxicity, and overall response [10]. Among the CYP enzymes, CYP2D6, CYP2C9, and CYP2C19 have garnered substantial attention due to their involvement in the metabolism of numerous clinically significant drugs. For instance, CYP2D6 is responsible for the metabolism of several antidepressants (e.g., selective serotonin reuptake inhibitors), antipsychotics (e.g., risperidone), and antiarrhythmic agents (e.g., flecainide) [11].

Genetic variations in CYP2D6 can lead to altered enzyme activity, resulting in the classification of individuals into different phenotypic groups, such as poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), or ultrarapid metabolizers (UMs) [12]. These phenotypic variations can impact drug concentrations, therapeutic outcomes, and the risk of adverse drug reactions(as illustrated in Table 1).

Table 1. the table provides a summary of genetic polymorphisms known to significantly impact drug response, outlining the associated drugs and the resulting clinical consequences

Genetic polymorphism	Drug (s) involved	Clinical consequences
CYP2D6 *4/*4	Codeine, Tamoxifen	Reduced drug metabolism, decreased efficacy
CYP2C19 *2/*2	Clopidogrel, Proton Pump, inhibitors	Impaired drug activation, reduced efficacy
VKORC1 -1639G>A	Warfarin	Altered sensitivity, risk of bleeding
HLA-B*5701	Abacavir (HIV drug)	Hypersensitivity reaction, severe adverse events
TPMT *2/*3A	Thiopurines (e.g., Azathioprine)	Increased risk of myelosuppression
UGT1A1 *28	Irinotecan	Increased risk of toxicity, neutropenia
HLA-B*1502	Carbamazepine	Risk of severe skin reactions, e.g., SJS/TEN
SLCO1B1 *5/*5	Statins (e.g., Simvastatin)	Increased risk of myopathy
NAT2 Slow Acetylator	Isoniazid, Hydralazine	Altered drug metabo lism, risk of toxicity
MTHFR C677T	Methotrexate	Altered folate metabo lism, efficacy concerns

Similarly, genetic variants in CYP2C9 are known to affect the metabolism of drugs such as warfarin, a widely prescribed anticoagulant. Variants in CYP2C9, particularly CYP2C9*2 and CYP2C9*3, are associated with reduced enzyme activity, resulting in decreased drug clearance and an increased risk of bleeding events in patients receiving warfarin therapy [13].

CYP2C19 is another crucial enzyme involved in the metabolism of numerous drugs, including proton pump inhibitors (e.g., omeprazole), selective serotonin reuptake inhibitors (e.g., escitalopram), and antiplatelet agents (e.g., clopidogrel). Genetic variations in CYP2C19 can lead to altered enzyme activity, resulting in distinct metabolizer phenotypes, with poor metabolizers being associated with reduced drug metabolism and potential treatment failure [14].

Apart from the CYP superfamily, other genetic variants can also impact drug metabolism pathways. For instance, the thiopurine methyltransferase (TPMT) gene plays a crucial role in the metabolism of thiopurine drugs like azathioprine and mercaptopurine, commonly used in the treatment of autoimmune diseases and malignancies. Variants in the TPMT gene, such as TPMT*2 and TPMT*3A, result in reduced enzyme activity, leading to higher drug concentrations and an increased risk of myelosuppression [15]. Genetic testing for TPMT variants before initiating thiopurine therapy allows for personalized dosing to optimize efficacy while minimizing toxicity.

Additionally, the uridine diphosphate glucuronosyltransferase (UGT) enzymes, particularly UGT1A1, are involved in the glucuronidation and subsequent elimination of drugs such as irinotecan, a widely used chemotherapeutic agent. A genetic variant in UGT1A1, known as UGT1A1*28, is associated with reduced enzyme activity, resulting in impaired drug clearance and an increased risk of severe myelosuppression and diarrhea in patients receiving irinotecan [16]. Prospective UGT1A1 genotyping can aid in dose adjustments and personalized treatment strategies to mitigate the risk of severe adverse reactions.

Moreover, the multidrug resistance protein 1 (MDR1) gene, also known as ATP-binding cassette sub-family B member 1 (ABCB1), encodes a drug efflux pump that plays a critical role in drug transport and elimination. Genetic variants in MDR1/ABCB1, such as C3435T and G2677T/A, have been associated with altered drug bioavailability and response to various medications, including anticancer drugs, immunosuppressants, and cardiovascular medications [17]. Understanding the impact of MDR1/ABCB1 genetic variants can assist in optimizing drug selection, dosing, and overall treatment outcomes.

III.Genetic biomarkers for drug efficacy and safety

The identification of genetic biomarkers has revolutionized the field of pharmacogenomics by enabling the prediction of drug response and individualizing treatment strategies. Genetic variants in specific genes have been associated with variations in drug efficacy and safety profiles, offering valuable insights into personalized medicine approaches [4].

The identification of genetic biomarkers for predicting drug response is a crucial step toward optimizing therapy. By examining specific gene variants, researchers have uncovered associations between genetic variations and drug response in various therapeutic areas. For instance, genetic variants in the human epidermal growth factor receptor 2 (HER2) gene have been found to predict the response to trastuzumab in breast cancer patients. The amplification or overexpression of HER2 is indicative of a favorable response to trastuzumab, enabling the selection of patients who are most likely to benefit from this targeted therapy [18].

Similarly, the presence of specific mutations in the BCR-ABL1 gene is used to identify chronic myeloid leukemia (CML) patients who are likely to respond to tyrosine kinase inhibitors such as imatinib [19].

Moreover, genetic markers associated with adverse drug reactions have shed light on the interplay between genetic variations and drug safety. For instance, the human leukocyte antigen (HLA) gene region has been implicated in severe cutaneous adverse drug reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, which can occur in response to medications such as carbamazepine and allopurinol. Certain HLA-B alleles, such as HLA-B*15:02 and HLA-B*57:01, have been identified as risk factors for these reactions, allowing for pre-treatment screening and the implementation of preventive measures [20].

Furthermore, pharmacogenomic studies have uncovered associations between specific gene variants and drug efficacy in diverse therapeutic areas. For example, variants in the VKORC1 and CYP2C9 genes have been linked to warfarin response and dosage requirements. Genetic testing for VKORC1 and CYP2C9 variants allows for individualized warfarin dosing to achieve optimal anticoagulation while minimizing the risk of bleeding or thromboembolic events [21].

Advancements in genomics have facilitated the discovery of genetic biomarkers associated with drug efficacy and safety across various therapeutic areas. For instance, in the field of oncology, the identification of genetic mutations in the epidermal growth factor receptor (EGFR) gene has revolutionized the treatment of non-small cell lung cancer (NSCLC). Specific EGFR mutations, such as exon 19 deletions and the L858R substitution, have been linked to increased sensitivity to EGFR tyrosine kinase inhibitors (TKIs) like erlotinib and gefitinib. Consequently, EGFR mutation testing has become an essential diagnostic tool for guiding treatment decisions in NSCLC, enabling the selection of patients who are more likely to respond favorably to targeted therapies [22].

Similarly, genetic biomarkers have been identified for predicting response to immunosuppressive medications used in transplantation. The gene encoding thiopurine S-methyltransferase (TPMT) plays a crucial role in the metabolism of thiopurine drugs such as azathioprine and mercaptopurine. Genetic variants in TPMT, such as TPMT*2 and TPMT*3A, are associated with reduced enzyme activity, leading to increased drug toxicity and a higher risk of myelosuppression. TPMT genotyping is now recommended prior to initiating thiopurine therapy to guide dosage adjustments and prevent severe adverse reactions [15].

Furthermore, the concept of pharmacogenomics has also extended to cardiovascular medicine. Genetic variations in the gene encoding the enzyme CYP2C19 have been associated with variable response to antiplatelet therapy with clopidogrel, commonly prescribed after percutaneous coronary intervention (PCI). Patients with loss-of-function alleles, such as CYP2C19*2, exhibit reduced activation of clopidogrel and may have an increased risk of adverse cardiovascular events. Genotyping for CYP2C19 variants allows for tailored antiplatelet therapy, with alternative agents like ticagrelor or prasugrel being recommended for patients with identified loss-of-function variants [23].

These examples underscore the clinical significance of genetic biomarkers in predicting drug response and guiding treatment decisions. The integration of pharmacogenomic information into routine clinical practice empowers healthcare providers to make personalized therapeutic choices based on an individual's genetic profile. By selecting the most effective and safe medications for each patient, pharmacogenomics has the potential to enhance treatment outcomes, minimize adverse events, and optimize the use of healthcare resources [2].

IV. Pharmacogenomic testing approaches

Pharmacogenomic testing plays a vital role in translating genetic information into actionable clinical insights, enabling personalized medicine approaches. Various techniques and methodologies are employed for pharmacogenomic testing, each with its own strengths and limitations [24]. Genotyping, which involves the analysis of specific genetic variants, is commonly used for pharmacogenomic testing. Techniques such as polymerase chain reaction (PCR), DNA microarrays, and next-generation sequencing (NGS) facilitate the detection of genetic variations associated with drug response [25]. PCR-based methods, including allele-specific PCR and real-time PCR, offer high specificity and sensitivity for targeted genotyping. DNA microarrays enable simultaneous testing for multiple genetic variants, while NGS allows for comprehensive analysis of the entire genome or specific gene regions [26].

Challenges and limitations exist in implementing pharmacogenomic testing in routine clinical practice. One significant challenge is the interpretation and clinical relevance of genetic variants. While many variants have been associated with drug response, not all have been definitively linked to clinical outcomes or have established therapeutic guidelines. Additionally, the presence of multiple genetic variants and the potential interactions among them further complicate interpretation [27]. Standardization of pharmacogenomic testing platforms, variant classification, and reporting guidelines are crucial for ensuring consistent and accurate results across different laboratories and clinical settings.

Another limitation is the cost-effectiveness of pharmacogenomic testing. The expenses associated with genetic testing, particularly with NGS-based approaches, can be a barrier to widespread implementation. However, as the costs of sequencing technologies continue to decline, and with the development of targeted genotyping panels, the economic feasibility of pharmacogenomic testing is improving [28].

Integration of pharmacogenomic testing into clinical practice poses another challenge. Healthcare professionals require education and training to understand the implications of pharmacogenomic test results, interpret them in the context of individual patient characteristics, and apply the information to guide treatment decisions [29]. Furthermore, the development of clinical decision support systems and electronic health record (EHR) integration is crucial for seamless integration of pharmacogenomic information into the clinical workflow. Realizing the full potential of pharmacogenomic testing requires collaboration among researchers, clinicians, laboratory professionals, and policymakers to address these challenges and facilitate widespread adoption.

Despite these challenges, efforts are underway to integrate pharmacogenomic testing into routine clinical care. Several institutions and healthcare systems have implemented pharmacogenomic testing programs, and guidelines and recommendations for specific drug-gene pairs have been developed by organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) [15]. Collaborative research initiatives are exploring the clinical utility and cost-effectiveness of pharmacogenomic testing, providing valuable evidence to guide its integration into routine care.

V. Clinical applications of pharmacogenomics

Pharmacogenomic testing has demonstrated its clinical utility in guiding drug therapy decisions, optimizing treatment outcomes, and improving patient safety. Several drugs have been identified for which pharmacogenomic testing is recommended to aid in personalized prescribing [30]. For instance, the anticoagulant drug warfarin has been extensively studied in the context of pharmacogenomics. Genetic testing for variants in the VKORC1 and CYP2C9 genes is recommended to predict individualized warfarin dosing requirements and minimize the risk of bleeding or thrombotic events [15]. Similarly, the antiplatelet agent clopidogrel requires pharmacogenomic testing for the CYP2C19 genotype to identify patients who may exhibit reduced drug response and guide the selection of alternative therapies like ticagrelor or prasugrel [23].

Case studies have illustrated the impact of pharmacogenomics on patient outcomes. One notable example is the use of pharmacogenomic testing in HIV/AIDS treatment. The Human Immunodeficiency Virus (HIV) can develop resistance to antiretroviral medications over time. However, genotypic testing for drug resistance-associated mutations can guide the selection of optimal antiretroviral regimens, improving treatment response and reducing virologic failure rates [31]. Additionally, in the field of psychiatry, pharmacogenomic testing for antidepressant and antipsychotic medications has shown promising results. Tailoring drug therapy based on individual genetic profiles has been associated with improved treatment response rates and reduced side effects, leading to enhanced patient outcomes in psychiatric disorders [32].

The implementation of pharmacogenomics varies across different healthcare settings. In specialized areas such as oncology, pharmacogenomic testing has become an integral part of treatment decisions. Tumor genomic profiling enables the identification of specific genetic alterations that drive tumor growth, guiding the selection of targeted therapies or clinical trial participation [33]. In primary care settings, pharmacogenomic testing is increasingly being adopted for drugs commonly prescribed, such as antidepressants and analgesics, to optimize treatment outcomes and improve patient safety [34]. Furthermore, pharmacogenomic testing has gained traction in the field of transplantation, where it assists in tailoring immunosuppressive therapy based on individual genetic profiles, thereby enhancing graft survival rates [35].

Efforts to integrate pharmacogenomics into routine clinical care have been supported by the development of guidelines and clinical decision support tools. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have provided evidence-based recommendations for specific drug-gene pairs, facilitating the interpretation of pharmacogenomic test results and guiding treatment decisions [36]. The integration of pharmacogenomics into electronic health records (EHRs) and clinical decision support systems is enabling healthcare providers to access and apply pharmacogenomic information seamlessly in their daily practice, enhancing the implementation of personalized medicine approaches.

The clinical applications of pharmacogenomics extend beyond specific drug-gene pairs. For instance, in the field of anesthesia, pharmacogenomic testing has shown promise in predicting individual responses to various anesthetic agents and analgesics. Genetic variants in genes encoding drug-metabolizing enzymes and drug targets can influence drug efficacy, side effects, and recovery time. Tailoring anesthetic and analgesic regimens based on individual genetic profiles may optimize pain management and minimize adverse events, leading to improved patient satisfaction and outcomes [37]. Furthermore, pharmacogenomic testing has demonstrated utility in psychiatric disorders such as major depressive disorder and schizophrenia. Antidepressants and antipsychotics exhibit variable response rates and side effect profiles among individuals. Pharmacogenomic testing can help identify genetic variations associated with drug metabolism and drug targets, assisting in the selection of appropriate medications and dosages for optimal therapeutic outcomes. This personalized approach to psychiatric medication management has the potential to improve treatment response rates and minimize the burden of side effects [38].

The implementation of pharmacogenomics in different healthcare settings has witnessed varying degrees of success. In specialized clinics and academic medical centers, where resources and expertise are readily available, pharmacogenomic testing programs have been effectively integrated into patient care workflows. Clinical decision support systems embedded within electronic health records assist healthcare providers in interpreting genetic test results and making informed treatment decisions based on available evidence and guidelines [39].

However, challenges persist in more resource-limited settings, where limited access to genetic testing infrastructure and lack of specialized expertise pose barriers to widespread implementation. Collaborative efforts among healthcare systems, regulatory bodies, and policymakers are essential to address these challenges and facilitate equitable access to pharmacogenomic testing.

Case studies and real-world evidence have highlighted the impact of pharmacogenomics on patient outcomes. For instance, a study examining the implementation of preemptive pharmacogenomic testing in a large healthcare system demonstrated significant reductions in adverse drug reactions and hospitalizations, leading to cost savings and improved patient care [9].

These examples underscore the potential of pharmacogenomic testing to enhance treatment outcomes, reduce healthcare costs, and improve patient safety across diverse clinical scenarios. As the field of pharmacogenomics continues to evolve, ongoing research and collaboration are necessary to expand the repertoire of drugs with pharmacogenomic implications and to refine guidelines for clinical implementation. Pharmacogenomic testing has the potential to transform healthcare by enabling personalized and precise medication selection and dosing, thus optimizing therapeutic outcomes and reducing the risk of adverse drug reactions.

VI. Ethical, legal, and social implications of pharmacogenomics

As pharmacogenomic testing becomes more prevalent, it raises important ethical, legal, and social considerations that must be addressed to ensure responsible and equitable implementation. One of the key concerns is the protection of patient privacy and the secure handling of genetic information. Given the sensitive nature of genetic data, robust privacy safeguards must be in place to prevent unauthorized access and misuse. Ethical frameworks emphasize the importance of informed consent, ensuring that patients understand the implications of genetic testing, the potential risks, and the limitations of test results. Healthcare providers and researchers must prioritize the secure storage and responsible use of genetic information, adhering to stringent data protection regulations and ethical guidelines [40]. The issue of health disparities and access to pharmacogenomic testing also requires attention. Genetic testing technologies and resources may not be equally available across diverse populations, leading to disparities in healthcare delivery and outcomes. Ensuring equitable access to pharmacogenomic testing is crucial to prevent exacerbating existing healthcare disparities. Efforts should focus on addressing barriers such as cost, infrastructure, education, and cultural sensitivity. Collaborations between stakeholders, including policymakers, researchers, healthcare providers, and patient advocacy groups, are necessary to develop strategies that promote inclusivity and mitigate disparities in the implementation of pharmacogenomics [30].

Policy and regulatory frameworks play a vital role in governing the ethical and responsible use of pharmacogenomic testing. National and international bodies have developed guidelines and regulations to guide the practice of pharmacogenomics. These frameworks address issues such as laboratory quality standards, reporting of test results, interpretation of genetic variants, and the integration of pharmacogenomic information into clinical practice. They aim to ensure the accuracy and reliability of test results, protect patient rights, and promote evidence-based decision-making. Policymakers should continuously evaluate and update these frameworks to keep pace with the evolving field of pharmacogenomics and address emerging ethical, legal, and social challenges [41].

Additionally, public engagement and education are crucial in fostering understanding and acceptance of pharmacogenomic testing. Public perceptions, beliefs, and attitudes toward genetic testing can influence its adoption and implementation.

Open dialogue between researchers, healthcare providers, policymakers, and the public can help address concerns, dispel misconceptions, and promote awareness about the benefits and limitations of pharmacogenomics. Furthermore, initiatives that promote health literacy and provide accessible educational resources can empower individuals to make informed decisions about genetic testing and participate actively in their healthcare [42].

Addressing the ethical, legal, and social implications of pharmacogenomics is paramount to ensure its responsible and equitable integration into clinical practice. By considering issues related to privacy, consent, access, and policy, healthcare systems can navigate the complexities of pharmacogenomics while safeguarding patient rights and promoting equal opportunities for improved treatment outcomes.

VII. Future directions and concluding remarks

Pharmacogenomics is a rapidly evolving field, and several future directions and challenges lie ahead as researchers and healthcare providers seek to maximize its potential. Advances in technologies and their application to pharmacogenomics are poised to shape the future of personalized medicine. The emergence of novel sequencing technologies, such as single-molecule sequencing and long-read sequencing, holds promise for more comprehensive and accurate genetic variant detection, enabling deeper insights into the relationships between genetic variations and drug response [43]. Moreover, the integration of multi-omics data, including genomics, transcriptomics, and metabolomics, can provide a more comprehensive understanding of individual variations in drug metabolism and response, offering a holistic approach to personalized therapeutics [44].

The seamless integration of pharmacogenomic information into electronic health records (EHRs) is crucial for realizing the full potential of personalized medicine. The inclusion of pharmacogenomic test results in EHRs allows healthcare providers to access and utilize genetic information at the point of care, facilitating informed treatment decisions and minimizing potential medication-related adverse events. Integration of pharmacogenomic data into EHRs can also enable clinical decision support systems to provide real-time alerts and tailored recommendations based on an individual's genetic profile, further enhancing precision medicine approaches [39].

Despite significant progress, there are several areas that require further research and development. One key area is the expansion of evidence-based guidelines for pharmacogenomic testing and interpretation. While guidelines for specific drug-gene pairs exist, there is a need for broader guidelines that encompass a wider range of drugs and genetic variations. Additionally, the translation of pharmacogenomic discoveries into clinical practice requires robust evidence on the clinical utility and cost-effectiveness of testing. Prospective studies evaluating the impact of pharmacogenomic-guided therapy on patient outcomes, healthcare utilization, and cost-benefit analysis are crucial to build a strong evidence base for widespread implementation [45].

Furthermore, addressing the challenges associated with data management and analysis is paramount. The integration and analysis of large-scale pharmacogenomic datasets, coupled with electronic health records, necessitate the development of robust bioinformatics tools and scalable infrastructure. Collaboration among researchers, bioinformaticians, and data scientists is essential to optimize data storage, processing, and interpretation, enabling efficient utilization of pharmacogenomic data for clinical decision-making [46].

Another important direction for future research is the exploration of additional genetic factors beyond single-nucleotide polymorphisms (SNPs). Copy number variations, epigenetic modifications, and gene-gene interactions are increasingly recognized as key contributors to interindividual variability in drug response. Understanding the complex interplay of these factors and their impact on pharmacogenomics will provide a more comprehensive understanding of individualized drug therapy and treatment outcomes [47].

In summary, the future of pharmacogenomics holds great promise in revolutionizing personalized medicine. Advances in technologies, integration into electronic health records, the development of evidence-based guidelines, and further research into genetic variations and interactions are crucial for the successful implementation of pharmacogenomics, enabling healthcare providers to deliver precise and individualized therapeutic interventions, ultimately improving patient outcomes.

Conflicts of interest

The author declare no conflicts of interest to declare.

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UPDATE

Evidence-based insights : a comprehensive review of the literature in general surgery

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KEY WORDS

General surgery ; Evidence-based insights ; Surgical techniques ; Minimally invasive surgery ; Surgical outcomes

Abstract

General surgery is a dynamic field that continues to witness significant advancements and innovation. This literature review aims to provide evidence-based insights into the latest developments and key findings in general surgery.

The review encompasses a comprehensive analysis of various subtopics, including historical perspectives, surgical techniques, advances in minimally invasive surgery, surgical oncology, trauma surgery, surgical infections and complications, emerging technologies, surgical education and training, quality improvement initiatives, and future directions. By synthesizing relevant literature, this review highlights the current state of knowledge, identifies research gaps, and explores potential areas for future research and clinical practice.

Through a critical examination of the literature, this review aims to offer surgeons, researchers, and healthcare professionals a comprehensive overview of the advancements in general surgery, facilitating informed decision-making and improving patient outcomes.

Introduction

General surgery, an ever-evolving field, is integral to diagnosing, treating, and managing numerous surgical conditions. Recent advancements in surgical techniques, technology, and perioperative care have significantly enhanced patient outcomes and surgical practices [1]. To maintain evidence-based decision-making and stay updated on the latest developments, it is essential for surgeons, researchers, and healthcare professionals to thoroughly understand the current state of knowledge in general surgery [2]. This literature review aims to critically analyze recent literature, offering insights into key topics and trends to guide clinical practice, stimulate further research, and promote innovative strategies.

The review provides a historical overview of general surgery, highlighting major milestones and breakthroughs, and traces the shift from traditional open surgery to minimally invasive procedures like laparoscopic and robotic-assisted surgeries. Surgical oncology, trauma surgery, and the prevention and management of surgical site infections and post-operative complications are critical areas explored. Emerging technologies such as artificial intelligence, virtual reality, and telemedicine are transforming surgical practice, enhancing precision and patient outcomes. Additionally, advancements in surgical education, including simulation-based training and quality improvement initiatives, are pivotal for the continuous development of surgical practice. The review also discusses future prospects, such as personalized medicine and precision surgery, aiming to bridge the gap between evidence and practice and empower clinicians to make informed decisions.

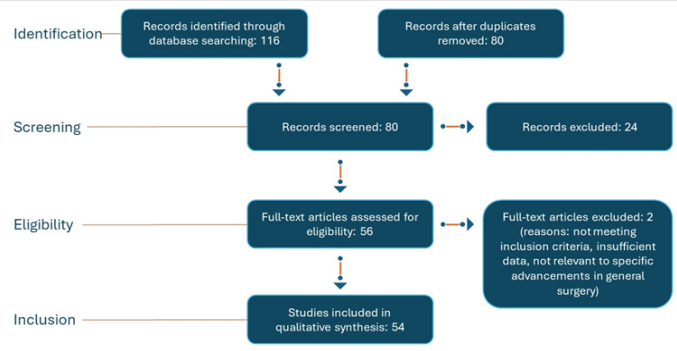
Methodology

A systematic approach was utilized for this literature review, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to gather relevant articles and studies on advancements in general surgery. A thorough search was conducted in reputable databases, including PubMed, Google Scholar, Scopus, and Web of Science, using specific keywords such as «surgical techniques,» «general surgery,» «minimally invasive surgery,» «surgical outcomes,» and «evidence-based insights» to ensure comprehensive coverage of pertinent literature.

The inclusion criteria for the studies were as follows: (1) publications in English, (2) studies focusing specifically on advancements in general surgery, and (3) studies reporting on informed decision-making and improved patient outcomes. Initially, 116 articles were retrieved from the databases. After a meticulous examination to eliminate duplicate references, 80 unique articles met the inclusion criteria. These articles underwent rigorous evaluation through a comprehensive assessment of their titles, abstracts, and full texts, confirming their alignment with the established inclusion criteria and warranting their inclusion in the review.

To provide a clear overview of the study selection process, the PRISMA flow diagram is included below (**Figure 1**), illustrating the number of records identified, screened, and included in the review, along with reasons for exclusion at each stage.

Figure 1 illustrates the PRIMSA flow diagram



I.HISTORICAL OVERVIEW OF GENERAL SURGERY

General surgery has a rich history that has evolved through centuries of medical advancements and surgical innovations. Understanding the historical developments in this field provides a valuable context for appreciating the current state of general surgery and its continued progress.The origins of surgery can be traced back to ancient civilizations, where early surgical procedures were primarily performed for wound management, bone setting, and basic surgical interventions. Ancient Egyptians, Greeks, and Romans made significant contributions to surgical knowledge, documenting their techniques and observations.

During the Middle Ages, surgical practices faced numerous challenges due to limited knowledge of anatomy, infection control, and anesthesia. However, notable surgeons such as Guy de Chauliac and Ambroise Paré laid the foundation for modern surgical techniques and principles. Paré's introduction of ligatures instead of cauterization for wound closure revolutionized surgical practice and reduced postoperative complications [3]. The 19th century witnessed remarkable advancements in general surgery. The introduction of anesthesia, pioneered by William Morton and Crawford Long, enabled surgeons to perform longer and more complex procedures with reduced patient discomfort and improved outcomes [4]. In addition, the discoveries of Louis Pasteur and Joseph Lister on the principles of antisepsis and asepsis significantly reduced surgical site infections and improved surgical safety.

The field of general surgery experienced a major breakthrough in the 19th century with the introduction of anesthesia, enabling surgeons to perform more complex procedures. The use of ether and chloroform as anesthetics revolutionized surgical practice and expanded the scope of surgical interventions [5].The advent of the 20th century brought remarkable advancements in surgical techniques and technologies.

The development of sterilization methods, such as steam auto-

claves, facilitated safer surgical procedures [6]. Surgeons like William Halsted, Harvey Cushing, and William Mayo made significant contributions to the fields of surgical oncology, neurosurgery, and specialized surgical techniques.

The mid-20th century saw the emergence of minimally invasive surgery. The introduction of laparoscopy and its subsequent refinement by gynecologists and general surgeons marked a significant shift in surgical approaches. Laparoscopic procedures offered benefits such as reduced postoperative pain, shorter hospital stays, and faster recovery.Further advancements in surgical techniques and technologies continued into the 21st century. Robotic-assisted surgery, pioneered by Intuitive Surgical's da Vinci system, allowed for enhanced precision, dexterity, and visualization during surgical procedures [7]. The integration of advanced imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), enabled surgeons to accurately diagnose and plan complex surgical interventions.

II.SURGICAL TECHNIQUES

General surgery encompasses a wide range of surgical techniques that have evolved over time, each with its own advantages, limitations, and outcomes. This section reviews and discusses three commonly employed surgical techniques in general surgery: open surgery, laparoscopic surgery, and robotic surgery.

Open surgery, also known as traditional or conventional surgery, involves making a large incision to access the surgical site. This technique provides direct visualization and tactile feedback to the surgeon, facilitating precise surgical maneuvers. It has been the gold standard for many surgical procedures and remains the preferred approach in certain complex cases, such as major abdominal surgeries, trauma surgeries, and cases requiring extensive tissue manipulation [8]. The advantages of open surgery include excellent exposure of the surgical field, versatility in handling various anatomical structures, and the ability to perform simultaneous multiple procedures or interventions. Additionally, it allows for direct control of bleeding and efficient management of complications during the procedure [9].

Laparoscopic surgery, also known as minimally invasive surgery or keyhole surgery, has revolutionized the field of general surgery. It involves accessing the surgical site through small incisions. A laparoscope, a thin tube with a camera and light source, is inserted to provide a magnified view of the surgical field on a monitor.

Surgical instruments are then inserted through additional small incisions, allowing the surgeon to perform the procedure with minimal tissue disruption. Laparoscopic surgery offers several advantages over open surgery, including reduced postoperative pain, shorter hospital stays, faster recovery, and improved cosmetic outcomes [10]. It has become the preferred approach for many procedures, such as cholecystectomy, appendectomy, and bariatric surgeries.

Further advancements in laparoscopic surgery include the development of single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES).

SILS involves performing the entire procedure through a single incision, usually in the umbilicus, resulting in improved cosmetic outcomes and potentially reduced postoperative pain [11]. NOTES takes minimally invasive surgery a step further by accessing the surgical site through natural orifices, such as the mouth, anus, or vagina, eliminating visible external scars altogether [12]. These innovative techniques continue to evolve, and ongoing research aims to refine their applications and overcome technical challenges.

Robotic surgery represents a significant technological advancement in general surgery. It combines the benefits of laparoscopic surgery with enhanced dexterity, precision, and control provided by robotic-assisted systems. The surgeon operates the robotic console, manipulating robotic arms that hold and control surgical instruments. The robotic system translates the surgeon's movements into precise surgical actions, offering increased range of motion and improved instrument stability. This technology has revolutionized certain procedures, such as prostatectomy and hysterectomy, allowing for improved surgical outcomes, reduced blood loss, and shorter recovery times [13]. However, robotic surgery requires specialized training, a dedicated surgical team, and costly equipment, which can limit its widespread adoption.

III.ADVANCES IN MINIMALLY INVASIVE SURGERY

Minimally invasive surgery has revolutionized the field of general surgery by offering patients less invasive alternatives to traditional open surgery. This section explores the latest advancements in minimally invasive surgery, specifically focusing on laparoscopic and endoscopic procedures, and their impact on patient outcomes, post-operative recovery, and overall surgical practice.

Laparoscopic surgery, also known as minimally invasive or keyhole surgery, involves accessing the surgical site through small incisions. The use of laparoscopes, which consist of a camera and light source, provides high-definition images of the surgical field, allowing surgeons to visualize and navigate the internal organs with precision. Laparoscopic procedures have become increasingly common in various specialties, including gastrointestinal surgery, gynecology, urology, and bariatric surgery [14]. The advantages of laparoscopic surgery over traditional open surgery include reduced postoperative pain, smaller incisions, faster recovery times, shorter hospital stays, and improved cosmetic outcomes [15]. Moreover, laparoscopic procedures have shown comparable or even superior outcomes in terms of perioperative morbidity and mortality compared to open surgery. Ongoing advancements in laparoscopic instruments, such as robotic-assisted systems and 3D visualization, have further enhanced the precision and capabilities of laparoscopic procedures.

Endoscopic procedures have also witnessed significant advancements in recent years. Endoscopy allows direct visualization and intervention within the body's hollow organs or cavities, such as the gastrointestinal tract, respiratory system, and urinary tract.

Endoscopic techniques, such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and percutaneous endoscopic gastrostomy (PEG), have revolutionized the diagnosis and management of various diseases [16]. The development of advanced imaging technologies, including high-definition endoscopes, narrow-band imaging, and confocal laser endomicroscopy, has improved the visualization and characterization of lesions, aiding in early detection and targeted treatment [17]. Additionally, therapeutic endoscopic interventions, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have enabled the minimally invasive removal of precancerous and early-stage cancerous lesions in the gastrointestinal tract, reducing the need for more invasive surgical procedures.

The impact of these advancements in minimally invasive surgery on patient outcomes and post-operative recovery has been significant. Reduced postoperative pain and smaller incisions result in decreased analgesic requirements and faster mobilization, leading to shorter hospital stays and quicker return to normal activities. Minimally invasive procedures also offer lower rates of wound infections, reduced blood loss, and decreased overall morbidity compared to open surgery [18]. Additionally, the cosmetic benefits of smaller incisions contribute to improved patient satisfaction and psychosocial well-being.

IV. SURGICAL ONCOLOGY

General surgery plays a crucial role in the multidisciplinary management of various types of cancers, including breast, colorectal, gastric, and hepatic cancers. This section discusses the advancements in surgical approaches, adjuvant therapies, and outcomes in surgical oncology.

Breast cancer is one of the most common malignancies worldwide, and surgical intervention is a cornerstone of its treatment. The surgical management of breast cancer has evolved significantly, with a shift towards breast-conserving surgery, also known as lumpectomy or partial mastectomy, as an alternative to mastectomy. Breast-conserving surgery aims to remove the tumor while preserving the cosmetic appearance of the breast. Sentinel lymph node biopsy, a minimally invasive technique, has also gained prominence in evaluating the spread of breast cancer to regional lymph nodes [19]. Advances in oncoplastic surgery have allowed for simultaneous breast reconstruction during cancer resection, further improving cosmetic outcomes and patient satisfaction. Additionally, neoadjuvant therapies, such as chemotherapy and targeted therapies, are increasingly being used to downsize tumors before surgery, enabling more conservative surgical approaches and improving overall outcomes.

Colorectal cancer represents a significant burden globally, and surgery plays a critical role in its management. Surgical techniques for colorectal cancer have evolved from open surgery to minimally invasive approaches, such as laparoscopic and robotic-assisted surgery. These techniques offer advantages such as reduced postoperative pain, shorter hospital stays, faster recovery, and comparable oncological outcomes to open surgery [20]. In selected cases, transanal minimally invasive surgery (TAMIS) or transanal total mesorectal excision (TaTME) techniques are employed for rectal cancer, allowing for precise dissection and sphincter preservation [21]. The utilization of enhanced recovery after surgery (ERAS) protocols, including optimized perioperative care, has further improved postoperative recovery and patient outcomes in colorectal cancer surgery.

Gastric cancer is another malignancy that requires surgical intervention as a primary treatment modality. The advent of minimally invasive techniques, such as laparoscopic and robotic gastrectomy, has gained traction in the surgical management of gastric cancer. These approaches offer reduced blood loss, shorter hospital stays, and comparable oncological outcomes to open surgery [22]. Lymph node dissection is a critical component of gastric cancer surgery, and extended lymphadenectomy has shown improved survival outcomes in selected patients [23]. Neoadjuvant chemotherapy or chemoradiotherapy followed by surgery has become the standard of care for locally advanced gastric cancer, allowing for downstaging of tumors and facilitating curative resection.

Hepatic cancer, including primary hepatocellular carcinoma and metastatic liver tumors, often requires surgical intervention for optimal disease control. Surgical resection remains the gold standard for the management of localized liver tumors, with advances in surgical techniques enabling extended liver resections and preservation of liver function [24]. In cases where surgical resection is not feasible, minimally invasive ablation techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA), have emerged as effective alternatives, providing local tumor control and prolonging survival in selected patients. The advent of portal vein embolization (PVE) has facilitated the surgical resection of initially unresectable liver tumors by inducing compensatory liver hypertrophy in the future remnant liver.

The integration of adjuvant therapies, such as chemotherapy, radiation therapy, and targeted therapies, with surgical interventions has significantly improved outcomes in surgical oncology. Multidisciplinary approaches, including tumor boards and personalized treatment strategies, ensure optimal patient care and individualized treatment plans based on tumor characteristics and patient factors.

V. TRAUMA SURGERY

Trauma surgery plays a critical role in the management of various types of injuries, ranging from blunt and penetrating trauma to polytrauma resulting from accidents or acts of violence. This section provides a review of the latest literature on trauma surgery, encompassing the evaluation and management of different types of injuries, resuscitation techniques, surgical interventions, and outcomes.

Effective evaluation and management of trauma patients require a systematic approach that prioritizes patient stabilization, timely interventions, and multidisciplinary collaboration. The Advanced Trauma Life Support (ATLS) guidelines provide a standardized framework for initial assessment, resuscitation, and decision-making in trauma care [25].

The primary survey focuses on identifying and addressing immediate life-threatening injuries, such as airway compromise, tension pneumothorax, cardiac tamponade, and massive hemorrhage. Following the primary survey, a thorough secondary survey is conducted to detect other injuries that may be less apparent but still significant.

Resuscitation techniques in trauma surgery aim to restore and maintain vital organ perfusion and oxygenation. The concept of damage control resuscitation has gained prominence, emphasizing early control of hemorrhage, fluid resuscitation guided by permissive hypotension, and transfusion strategies aiming for balanced ratios of blood products [26]. The administration of tranexamic acid, an antifibrinolytic agent, has shown benefits in reducing mortality due to bleeding in trauma patients [27]. The use of goal-directed resuscitation strategies, such as point-of-care ultrasound and hemodynamic monitoring, allows for real-time assessment and optimization of the patient's hemodynamic status.

Surgical interventions in trauma surgery vary depending on the type and severity of injuries. Penetrating injuries may require exploratory laparotomy, thoracotomy, or neck exploration, depending on the anatomical location and suspected injuries [28]. Blunt injuries, including fractures, solid organ injuries, and traumatic brain injuries, often necessitate a multidisciplinary approach involving orthopedic surgery, neurosurgery, and interventional radiology. The adoption of minimally invasive techniques, such as laparoscopy and endovascular procedures, has expanded the range of injuries amenable to non-operative management, thereby reducing the need for extensive surgical interventions. The outcomes in trauma surgery depend on various factors, including the severity of injuries, promptness of interventions, and quality of postoperative care. The concept of damage control surgery emphasizes initial control of hemorrhage and contamination, followed by definitive surgical procedures once the patient's condition stabilizes [29]. The implementation of trauma systems and regional trauma centers, facilitating coordinated care and specialized expertise, has been associated with improved outcomes and reduced mortality rates. Additionally, advancements in critical care management, including targeted temperature management, nutrition support, and early mobilization, contribute to better long-term outcomes and functional recovery in trauma patients.

VI. SURGICAL INFECTIONS AND COMPLICATIONS

Surgical site infections (SSIs) and post-operative complications represent significant challenges in the field of surgery. This section explores the prevention, diagnosis, and management of SSIs, post-operative complications, and strategies to enhance patient safety and reduce morbidity and mortality.

Preventing SSIs requires a multifaceted approach that addresses various risk factors. Patient optimization plays a crucial role in reducing the likelihood of SSIs. This includes preoperative screening for comorbidities, such as diabetes and obesity, and optimizing these conditions to minimize the risk of infection [30].

Additionally, meticulous attention to surgical site preparation, including proper hair removal techniques and appropriate use of antiseptic solutions, helps reduce microbial colonization and subsequent infection [31]. Maintaining normothermia during surgery, through the use of warming devices, is also important in preventing SSIs, as hypothermia can impair the immune response.

In the diagnosis of surgical site infections, clinical assessment alone may not always provide a definitive diagnosis. Ancillary investigations, such as wound cultures and histopathological examination, can aid in identifying the causative organisms and determining the severity of the infection [32]. Moreover, advancements in imaging techniques, such as ultrasound and magnetic resonance imaging (MRI), have improved the detection of deep-seated infections and abscesses, facilitating timely intervention [33]. The implementation of surveillance programs and standardized definitions for surgical site infections, such as those established by the Centers for Disease Control and Prevention (CDC), allows for consistent monitoring and benchmarking of infection rates.

The management of surgical site infections involves a multidisciplinary approach. Early initiation of empirical antibiotic therapy, guided by local antimicrobial resistance patterns, is essential in controlling the infection. Once the causative organism is identified, targeted antimicrobial therapy can be administered [34]. In cases of extensive infection, surgical interventions such as wound debridement and drainage may be necessary to remove infected tissues and promote healing. Collaboration with infectious disease specialists can provide valuable expertise in managing complex infections and tailoring antimicrobial therapy.

Post-operative complications encompass a wide range of adverse events that can occur after surgery. Prompt recognition and early intervention are crucial in mitigating the impact of these complications on patient outcomes. Structured post-operative monitoring, including regular assessment of vital signs, laboratory values, and clinical parameters, helps detect complications at an early stage. Prompt intervention, such as surgical exploration or interventional procedures, may be required for complications such as hemorrhage, anastomotic leaks, or intra-abdominal abscesses [35]. Multidisciplinary collaboration, involving surgeons, intensivists, and allied healthcare professionals, ensures comprehensive management and optimal patient outcomes.

Strategies to improve patient safety and reduce morbidity and mortality in surgical practice encompass both systemic approaches and procedural interventions. Systemic approaches include the implementation of surgical safety checklists, which provide a standardized framework for ensuring critical safety steps are followed during surgery [36]. Team training programs, such as simulation-based training and crisis resource management, promote effective communication, teamwork, and decision-making in high-stress situations [37]. Procedural interventions, such as the use of intraoperative imaging techniques (e.g., fluoroscopy, intraoperative ultrasound), aid in real-time assessment and enhance surgical precision, reducing the risk of intraoperative complications.

VII.EMERGING TECHNOLOGIES IN GENERAL SURGERY

Emerging technologies such as artificial intelligence (AI), virtual reality (VR), and telemedicine are transforming various aspects of general surgery. AI has the potential to enhance diagnostic accuracy, surgical planning, and post-operative care by analyzing large datasets and aiding in the interpretation of radiological images [38]. Machine learning algorithms can predict surgical outcomes and identify high-risk patients, allowing for personalized treatment plans. AI-powered robotic surgery systems offer enhanced precision and reduced invasiveness. However, challenges like the need for high-quality data, algorithm transparency, and ethical considerations must be addressed [39].

Virtual reality (VR) technology provides immersive and interactive experiences for surgical training, pre-operative planning, and intraoperative guidance. VR simulations allow trainees to practice surgical techniques in a realistic virtual environment, promoting skill acquisition and reducing the learning curve [40]. Pre-operative VR models enable surgeons to visualize patient-specific anatomy, enhancing surgical planning and facilitating intraoperative navigation. Intraoperative VR guidance systems provide real-time feedback and facilitate precise surgical interventions [41]. Despite these advantages, challenges such as cost, availability, and integration with existing workflows need to be considered for the widespread implementation of VR in general surgery.

Telemedicine improves access to surgical care through remote consultations and post-operative follow-up. Teleconsultations allow surgeons to remotely evaluate patients, provide recommendations, and triage cases, reducing the need for travel and improving access to specialized care, especially in underserved areas [42]. Telemonitoring platforms facilitate remote monitoring of post-operative patients, enabling early detection of complications and timely interventions. However, ensuring data security, maintaining patient privacy, and addressing technical challenges like reliable connectivity are important considerations for the successful implementation of telemedicine in general surgery [43]. Integration of these technologies offers benefits such as improved diagnostic accuracy, enhanced surgical planning, and increased surgical precision, contributing to better patient outcomes and reduced complications. However, initial costs, specialized training, regulatory compliance, and seamless integration into existing systems remain challenges to be addressed [44].

VIII. SURGICAL EDUCATION AND TRAINING

Surgical education plays a vital role in preparing future surgeons for the complexities of their profession. This section reviews the literature on surgical education, encompassing residency training programs, simulation-based training, competency assessment, and the integration of technology in surgical education.

Residency training programs serve as the foundation for surgical education, providing structured and comprehensive training to aspiring surgeons. The Accreditation Council for Graduate Medical Education (ACGME) sets the standards for residency training, outlining the required competencies and educational milestones [45].

Residency programs typically involve a progressive curriculum, with trainees gradually assuming more responsibility under the supervision of experienced faculty members. Exposure to a diverse range of surgical cases, rotations in different subspecialties, and active participation in surgical procedures form the core components of surgical residency training.

Simulation-based training has emerged as a valuable tool in surgical education, allowing trainees to develop and refine surgical skills in a controlled environment. Virtual reality simulators, task trainers, and cadaveric models provide opportunities for deliberate practice and mastery learning [46]. Simulation-based training enables trainees to acquire technical skills, enhance decision-making abilities, and improve communication and teamwork in complex surgical scenarios. Additionally, simulators allow trainees to experience rare or high-risk situations that may be infrequently encountered in clinical practice, thus promoting patient safety and reducing potential harm [47]. Integration of simulation into surgical training curricula has been associated with improved performance and reduced patient complications.

Competency assessment is a critical component of surgical education, ensuring that trainees meet the necessary standards before progressing to independent practice. Objective assessment tools, such as the Objective Structured Assessment of Technical Skills (OSATS) and global rating scales, facilitate the evaluation of technical proficiency, communication skills, and professionalism [48]. Entrustable Professional Activities (EPAs), defined tasks that trainees are entrusted to perform autonomously, have gained prominence as a competency-based framework for assessing trainee progress. Regular formative and summative assessments, including direct observation, constructive feedback, and milestone evaluations, aid in monitoring trainee development and identifying areas for improvement.

The integration of technology in surgical education has transformed traditional teaching methods. Digital platforms, such as online modules, webinars, and surgical video libraries, provide easily accessible resources for trainees to acquire knowledge and enhance procedural understanding [49]. Web-based educational platforms, virtual classrooms, and teleconferencing allow for remote learning, fostering collaboration and knowledge exchange among trainees and educators [50]. Additionally, the use of augmented reality (AR) and virtual reality (VR) in surgical education enables immersive and interactive experiences, enhancing the acquisition of technical skills, surgical planning, and intraoperative guidance.

Incorporating interprofessional education and teamwork training in surgical education programs is also essential. Collaboration with other healthcare professionals, such as anesthesiologists, nurses, and allied health professionals, fosters a multidisciplinary approach and promotes effective communication and teamwork in the operating room [51]. Interprofessional simulations and team-based exercises facilitate the development of non-technical skills, such as leadership, communication, and situational awareness, which are crucial in providing safe and high-quality surgical care.

IX. QUALITY IMPROVEMENT IN GENERAL SURGERY

Quality improvement initiatives and patient safety measures are crucial components of general surgery to optimize surgical outcomes, enhance healthcare delivery, and improve patient satisfaction. This section discusses the importance of quality improvement in general surgery and highlights evidence-based guidelines that guide best practices.

Quality improvement in general surgery involves the systematic assessment and improvement of healthcare processes to ensure safe, effective, and patient-centered care. It encompasses various aspects, such as surgical site infection prevention, perioperative antibiotic prophylaxis, pain management, and timely interventions for complications. Quality improvement initiatives aim to reduce variations in care, enhance patient outcomes, and improve the overall quality of surgical services [52].

Patient safety measures play a vital role in quality improvement efforts. Implementation of surgical safety checklists, such as the World Health Organization's Surgical Safety Checklist, has been shown to reduce surgical complications and mortality rates [53]. These checklists provide a standardized framework for ensuring critical safety steps are followed during surgical procedures, including pre-operative verification, site marking, and intraoperative pause for critical moments. Furthermore, the reporting and analysis of adverse events and near misses through incident reporting systems help identify system vulnerabilities and implement preventive measures.

Evidence-based guidelines serve as a foundation for quality improvement in general surgery. They are developed through rigorous analysis of available research evidence, expert consensus, and consideration of patient preferences. Guidelines address various aspects of surgical care, including preoperative evaluation, surgical techniques, post-operative management, and long-term follow-up [54]. They provide recommendations for best practices, risk reduction strategies, and interventions to improve patient outcomes.

One example of evidence-based guidelines in general surgery is the Enhanced Recovery After Surgery (ERAS) protocols. These protocols provide multimodal perioperative care pathways designed to optimize patient outcomes, reduce complications, and accelerate recovery. ERAS protocols encompass interventions such as preoperative patient education, preoperative fasting optimization, goal-directed fluid therapy, minimally invasive surgical techniques, early mobilization, and enhanced pain management strategies. Implementation of ERAS protocols has been associated with decreased length of hospital stay, reduced complications, and improved patient satisfaction.

Another key aspect of quality improvement in general surgery is the use of performance metrics and quality indicators. These measures provide objective data to assess and monitor the quality of surgical care. Examples of performance metrics include surgical site infection rates, readmission rates, surgical complication rates, and compliance with evidence-based practices. Regular monitoring of these metrics allows for the identification of areas requiring improvement and the implementation of targeted interventions.

X. FUTURE DIRECTIONS, CHALLENGES, AND CONCLUDING REMARKS

In General surgery continues to evolve in response to advancements in technology, research, and changing healthcare needs. This section highlights current challenges, future directions, and the importance of interdisciplinary collaborations in shaping the future of general surgery.

One of the emerging areas in general surgery is personalized medicine. Advances in genomics, proteomics, and molecular diagnostics offer opportunities for tailored treatment strategies based on an individual's genetic profile, allowing for precise identification of genetic predispositions, prognosis, and selection of targeted therapies. Personalized medicine holds the potential to optimize patient outcomes, reduce complications, and improve treatment efficacy in surgical practice. However, challenges such as the integration of genomic data into clinical decision-making, standardization of testing methodologies, and ethical considerations surrounding data privacy and consent need to be addressed.

Precision surgery, encompassing minimally invasive techniques, image-guided interventions, and robotic surgery, continues to advance. The integration of advanced imaging modalities, such as intraoperative MRI and fluorescence-guided surgery, allows for real-time visualization and precise identification of anatomical structures and pathological targets, improving surgical accuracy. Robotics and computer-assisted technologies enhance surgical dexterity, provide enhanced visualization, and enable complex procedures with reduced invasiveness. As precision surgery evolves, challenges such as cost, access to technology, and training requirements need to be considered to ensure equitable adoption and optimal outcomes.

Interdisciplinary collaborations are increasingly important in general surgery. Collaboration with specialists from various fields, including radiology, oncology, pathology, and genetics, facilitates comprehensive patient management, fosters a multidisciplinary approach, and ensures the delivery of high-quality, patient-centered care. Interdisciplinary tumor boards, where experts from different disciplines discuss complex cases and develop integrated treatment plans, have become a cornerstone of cancer care. Moreover, collaborations with data scientists, bioengineers, and informaticians are essential in harnessing the power of big data, artificial intelligence, and predictive analytics to improve surgical decision-making, optimize resource allocation, and enhance patient outcomes. Challenges persist in the field of general surgery. Access to surgical care remains a global concern, particularly in underserved regions. Addressing healthcare disparities and ensuring equitable access to surgical services is a crucial challenge that requires innovative solutions, including telemedicine, task shifting, and surgical capacity building initiatives. Additionally, the rapid pace of technological advancements poses challenges in keeping up with evolving surgical techniques, maintaining proficiency, and incorporating new technologies into clinical practice. Continuous professional development, lifelong learning, and standardized training frameworks are essential to address these challenges.

Conclusion

In conclusion, the future of general surgery lies in the realms of personalized medicine, precision surgery, and interdisciplinary collaborations. Embracing the potential of personalized medicine to tailor treatment strategies, advancing precision surgery techniques, and fostering interdisciplinary collaborations will contribute to improved patient outcomes, enhanced surgical care delivery, and optimized resource utilization.

However, addressing challenges such as the integration of genomic data, cost considerations, and ensuring equitable access to surgical care will be crucial in realizing the full potential of these advancements.

Competing interests

The author declare no conflict of interest.

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CAS CLINIQUE

Intussusception of the small intestine due to an intestinal melanoma metastasis : a case report & literature review

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KEY WORDS

Melanoma, Metastasis, Intussusception, Surgery, Intestinal obstruction, Emergency

Abstract

Intussusceptions of the small intestine in adults is very rare and represents only 1% of all cases of intestinal obstruction; this condition is rarely described in the literature. Surgery is the procedure of choice in most cases.

We report a case of ileo-ileal intussusceptions secondary to a melanoma metastatic tumor, occurring 4 years after surgery for malignant melanoma of the cheek.

The diagnosis of intussusception was confirmed by abdominal CT-Scan. However, only palliative surgery was feasible for this patient. At seven months after his surgery, the patient is alive and in good general condition. Intussusception in adults is the main clinical presentation indicative of intestinal metastasis from malignant melanoma. After our review of the literature, it seems that this complication occurs mainly in male patients and the site of predilection for this metastasis is the jejunum.

Introduction

Small bowel intussusception in adults is very rare and represents 1% of all acute bowel obstruction cases, with only 5% of all intussusception cases being diagnosed in adults [1, 2]. It is usually caused by benign or neoplastic bowel lesions [3, 4].

However, most small intestine obstructions due to tumor-induced intussusception remain rare; therefore, intussusception caused by melanoma metastases has rarely been described in the literature. Surgery is the preferred management option for such complications [1, 2].

Here, we present a case of a 45-year-old man with ileo-ileal intussusception caused by metastatic melanoma four years after he had undergone excision of a malignant melanoma on the left cheek.

Observation

A 42-year-old man was admitted to our emergency department for acute intestinal obstruction. The patient had complained of abdominal pain, nausea, and intermittent vomiting for two weeks before admission. These symptoms worsened with increasingly frequent vomiting, abdominal distension, and complete cessation of intestinal transit. Indeed, four years prior, the patient had undergone resection of malignant cutaneous melanoma of the left cheek, followed by chemotherapy. It's important to note that no lymphadenectomy was performed during the initial surgery.

Upon admission, the patient's general condition was slightly altered, with a blood pressure of 120/70 mmHg, a pulse of 90 beats per minute, and abnormal blood test results: white blood cell count elevated to 16,000/ml, hemoglobin at 8.96 g/dl, prothrombin level at 89%, blood urea at 0.80 g/l, creatinine at 11.70 mg/l, hyponatremia at 128 meq/l, and potassium level at 4.1 meq/l.

A standard abdominal X-ray revealed air-fluid levels indicative of small bowel obstruction. Abdominal computed tomography (CT-scan) confirmed that the cause of this acute intestinal obstruction was an intussusception associated with an ileal tumor, along with satellite metastatic lymphadenopathy (**Figure 1**).

Urgently admitted to the operating room, the patient underwent an open approach with a midline laparotomy. Exploration revealed an ileo-ileal intussusception caused by an ileal tumor (**Figure 2**), along with other tumor localizations and multiple lymphadenopathy (**Figure 3**). Surgical reduction of the invaginate loop was performed, revealing a dark black tumor causing intussusception, along with mesenteric lymphadenopathy. Similar but smaller tumors were found in the small intestine (**Figure 4**).

A palliative surgery involved resection of the invaginate ileal loop followed by end-to-end anastomosis due to the presence of several unresected metastases in the intestine. The postoperative stay was uneventful, and the patient was discharged on the 7th postoperative day.

The final histological examination of the resected specimen revealed that the intussusception was caused by a metastasis of a malignant melanoma measuring 85 mm in diameter. The microscopic examination described a malignant tumor proliferation made up of melanocyte cells infiltrating the entire intestinal wall with respect for the intact serosa; the resection margins were free. Invasion of two lymph nodes by the same proliferation was also noted. Immuno-histochemical staining confirmed that the tumor was a metastatic melanoma, and this tumor was BRAF mutated status.

After discussion, the multidisciplinary committee decided to refer the patient to oncology for chemotherapy based on a Dacarbazine regimen. At 7 months post-surgery, the patient remains alive and in good general condition.

Figure 1. CT-Scan : small bowel intussusception

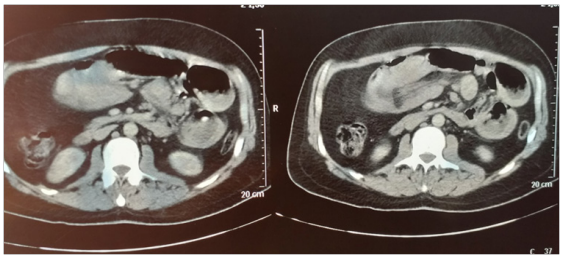


Figure 2. Ileo-ileal intussusception & tumor

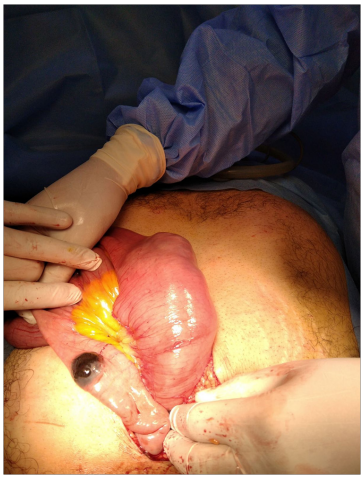


Figure 3. Other tumor localization

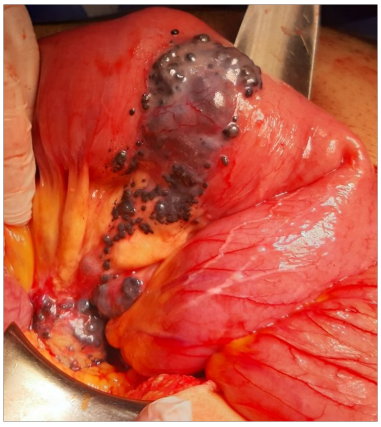
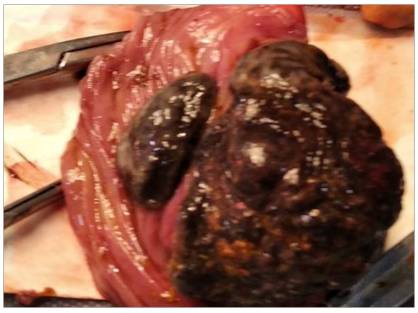


Figure 4. Appearance of the tumor after resection



Discussion

Intussusception in adults accounts for only 1% of cases of intestinal obstruction [5], while malignant gastrointestinal melanoma represents 1% of malignant tumors, with most being primary tumors that metastasize from the skin [6]. Hintz concluded that malignant cutaneous melanoma is the most frequent extra-digestive tumor to metastasize to the digestive tract several years later [7]. This is evident in our patient, who had a skin tumor on the left cheek treated four years ago with chemotherapy after surgical excision.

However, up to 60% of patients with gastrointestinal metastases are never diagnosed during their lifetime [8]. The symptoms are often nonspecific, including abdominal pain, vomiting, and sometimes indicative of intestinal obstruction [5]. Dokić reported a case of deep anemia associated with melena [9].

In our patient, intestinal intussusception was suspected on abdominal CT-scan. The diagnosis of intussusception was primarily made through abdominal CT-scan in most cases described in the literature [5, 6, 9].

Acute intestinal obstruction is a surgical emergency. Surgical exploration confirms intussusceptions and provides information about the extension and location of the disease. Surgery also allows for the treatment of acute intestinal obstruction by excising the digestive segment containing the metastasis that caused intussusception.

This can prevent recurrence and reduce symptoms. While the majority of authors use open surgery for these patients, some recent reports describe successful treatment with laparoscopic procedures [6,10]. We emphasize the importance of haptic sensation to detect small, often endo-luminal, and palpable but not visible metastases.

The median survival of patients operated on for digestive metastases of melanomas was 9.5 months, with a 5-year survival rate not exceeding 9%, according to Caputy et al [11]. After analyzing his series of 41 patients, he identified factors predicting poor prognosis in operated patients, such as the rapid appearance of metastases after treatment of the primary tumor (less than two years), the presence of small bowel metastasis, and a low patient's performance status [11].

In cases of widespread metastases, palliative chemotherapy becomes essential. It aims to alleviate symptoms, enhance quality of life, and possibly extend survival. In case of metastatic melanoma, chemotherapy options like dacarbazine, temozolomide, or immune checkpoint inhibitors are recommended. While not curative, palliative chemotherapy can manage symptoms and slow disease progression [12].

The table 1 summarizes similar cases published over the past five years, identified through a PubMed search using the keywords: melanoma, metastasis, intussusceptions.

Table 1. The following table summarizes similar cases published over the past five years

Author(year)	Country	Gender (age)	Delay after melanoma surgery	Localisation of metastasis	Localisation of intussusception	Management	Outcomes
Giakoustidis et al (2017)	Greece	F (45 yrs)	7 years	jejunum	Jejuno-jejunal	Resection & anastomosis (open)	3 years (Alive)
Hintze et al (2017)	Ireland	F (71 yrs)	9 years	Disseminated	Multiple	Reduction (laparoscopy converted to open)	9 months (Died)
Mahir (2017)	Russia	M (73 yrs)	6 years	Disseminated	Ileo-ileal	Reduction + ileo-transverse derivation (open)	2 months (Alive)
Miyazawa et al (2017)	Japan	M (85 yrs)	18 months	Disseminated	Ileao-coecal	?	2 months (Died)
Silva et al (2018)	Portugal	M (71 yrs)	7 years	ileum	Ileo-ileal	Resection and anastomosis (open)	31 months (Died)
Dokić et al (2018)	Slovenia	M (71 yrs)	7 years	Jejunum	Jejuno-jejunal	Reduction + enterotomy and tumor resection (open)	?
Butt et al (2019)	U.S.A	F (46 yrs)	11 years	Jejunum	Jejuno-jejunal	Resection (open)	6 months (Alive)
Ahmed et al (2019)	U.S.A	F (45 yrs)	5 years	Jejunum	Jejuno-jejunal	Resectio (Laparoscopy)	?
Kumano et al (2020)	Japan	F (71 yrs)	5 years	Jejunum	Jejuno-jejunal	Resection and anastomosis (Laparoscopy)	1 year (Alive)
Warschauer et al (2020)	Italy	M (73 yrs)	5 years	Jejunum	Jejuno-jejunal	Resection and anastomosis (Laparoscopy)	?
Yoneaga et al (2021)	Japan	M (85 yrs)	15 months	Disseminated	Multiple	Resection (open)	?
Correia de Sá et al (2021)	Portugal	M (71 yrs)	2 years	Jejunum	Jejuno-jejunal	Resection and anastomosis (open)	? (Died)
Yagmur et al (2021)	Turkey	M (71 yrs)	4 years	Jejunum	Jejuno-jejunal	Resection and anastomosis (Laparoscopy)	?
Mesli et al (2022)	Algeria	M (46 yrs)	4 years	Disseminated	Ilei-ileal	Resection and anastomosis (open)	7 months (Alive)

Conclusion

Intussusception in adults secondary to a metastatic tumor is a rare cause of small bowel obstruction. Our case, involving a metastatic melanoma originating from a cutaneous lesion on the left cheek excised four years earlier, highlights the rarity and complexity of this condition. However, the prognosis for such cases remains poor, further compounded by the presence of unresected metastatic localization in our patient.

Competing interests

The authors declare no conflict of interest.

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CAS CLINIQUE

Résection chirurgicale d'une volumineuse tumeur fibreuse solitaire de la plèvre

Surgical resection of a large solitary fibrous tumour of the pleura

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MOTS CLÉS

tumeur fibreuse solitaire, résection complète

Résumé

Introduction-Les tumeurs fibreuses solitaires sont des tumeurs bénignes mésenchymateuses rares, développées le plus souvent aux dépends de la plèvre. Elles surviennent plus fréquemment après 40 ans. Le fibrome pleural est le plus souvent asymptomatique ce qui explique leur caractère volumineux.

Nous rapportons un cas de tumeur pleurale volumineuse diagnostiqué chez un patient de 77 ans aux antécédents de diabète et d'hypertension artérielle. La découverte était faite sur une radiographie thoracique motivée par une toux intermittente évoluant depuis un mois.

La tomodensitométrie montrait une masse tumorale pleurale gauche mesurant 18 cm de grand axe, présentant un contact avec l'aorte descendante à l'origine d'un collapsus pulmonaire quasi-total. Une biopsie transpariétale a été réalisée et l'étude histologique revenait en faveur d'une tumeur fibreuse solitaire. L'exploration chirurgicale a révélé une tumeur volumineuse prenant naissance de la plèvre viscérale, sans contact intime avec les gros vaisseaux.

Les tumeurs fibreuses solitaires de la plèvre sont des tumeurs mésenchymateuses extrêmement rares et représentent moins de 5% de toutes les tumeurs pleurales, de diagnostic parfois difficile.

Conclusion-Le traitement de choix de ces tumeurs fibreuses solitaires est la résection chirurgicale complète, souvent sous thoracotomie, à cause de leur taille élevée. La récidive locale est rapportée dans 1,4 à 12 % en cas de résection incomplète.

KEY WORDS

solitary fibrous tumour, complete resection

Abstract

Introduction-Solitary fibrous tumours are rare benign mesenchymal tumours that most often develop at the expense of the pleura. They occur more frequently after the age of 40. Pleural fibromas are usually asymptomatic, which explains their large size.

We report a case of bulky pleural tumour diagnosed in a 77-year-old patient with a history of diabetes and arterial hypertension. The tumour was discovered on chest X-ray, after a month of intermittent coughing. A CT scan showed a left pleural tumour mass measuring 18 cm in long axis, in contact with the descending aorta, causing almost total lung collapse. A transparietal biopsy was performed and the histological study was in favour of a solitary fibrous tumour. Surgical exploration revealed a large tumour arising from the visceral pleura, without intimate contact with the large vessels.

Solitary fibrous tumours of the pleura are extremely rare mesenchymal tumours, accounting for less than 5% of all pleural tumours, and are sometimes difficult to diagnose.

Conclusion-The treatment of choice for these solitary fibrous tumours is complete surgical resection, often under thoracotomy because of their often large size. Local recurrence is reported in 1.4 to 12% of cases of incomplete resection.

Introduction

Les tumeurs fibreuses solitaires sont des tumeurs bénignes mésenchymateuses rares, développées aux dépens des séreuses. La localisation pleurale est la plus fréquente. Elles surviennent à tout âge, mais plus fréquemment après 40 ans. Elles sont le plus souvent asymptomatiques ce qui explique leur caractère volumineux. [1]. Nous rapportons un cas de tumeur fibreuse solitaire volumineuse de la plèvre (TFSP), diagnostiquée chez un patient en bon état général.

Observation

Un patient âgé de 77 ans, menuisier de profession, aux antécédents d'hypertension artérielle et de diabète type 2, s'était présenté dans notre consultation pour investigation d'une image thoracique pathologique. L'interrogatoire révélait que suite à une toux intermittente évoluant depuis un mois, une radiographie thoracique a été faite mettant en évidence une opcité ronde occupant la totalité de l'hémithorax gauche (**Figure 1**).

L'examen clinique retrouvait un patient en bon état général, sans signes de gravité. La tomodensitométrie thoracique montrait une masse tumorale pleurale gauche mesurant 18 cm de grand axe sur 10 cm de largeur. Cette formation était le siège de calcifications intra lésionnelles, en contact avec l'aorte descendante et l'artère pulmonaire gauche, à l'origine d'un collapsus pulmonaire quasi-total (**Figure 2**).

L'étude histologique des prélèvements biopsiques, réalisés sous contrôle scannographique, a conclu à une tumeur fibreuse sans signes de malignité.

La décision d'une résection chirurgicale après préparation du patient sur le plan respiratoire, a été prise en Réunion de Concertation Pluridisciplinaire (RCP).L'exploration chirurgicale a révélé une tumeur volumineuse prenant naissance de la plèvre viscérale au niveau de la grande scissure, sans contact intime avec les gros vaisseaux. Une dissection a été entreprise pour libérer la tumeur du poumon et de la paroi permettant une résection complète (**Figure 3**).

La résection du parenchyme pulmonaire n'était pas nécessaire et les suites opératoires étaient simples.

L'étude histologique de la pièce opératoire a montré une formation tumorale mesurant 22/18/9 cm, faite d'une prolifération tumorale de nature mésenchymateuse, de densité cellulaire faible à modérée, faite de faisceaux enchevêtrés de cellules ovoïdes régulières monomorphes sans nucléoles évident, baignant dans un fond collagénique fibreux. Il a été noté des figures mitotiques avec absence de nécrose.

L'immunohistochimie a montré une positivité du CD34,Bcl2 et de l'EMA ; une négativité de Ps100. Une décision de surveillance sans traitement adjuvant a été prise au sein de la RCP. Après un recul de deux ans, le patient est en bon état général, sans aucune récidive locale ou à distance.

Figure 1. Radiographie thoracique montrant une opacité homogène occupant l'hémithorax gauche refoulant le médiastin à droite

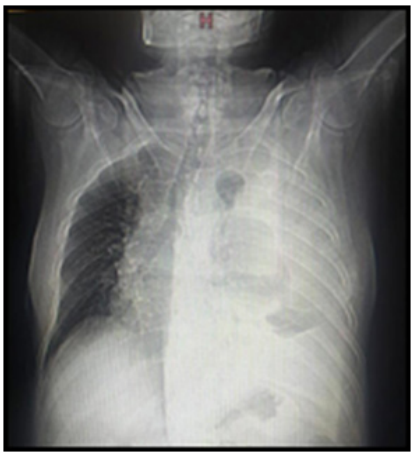


Figure 2. Tomodensitométrie thoracique montrant une masse tumorale pleurale gauche mesurant 18 cm de grand axe, contenant des calcifications et comprimant complètement le poumon gauche.

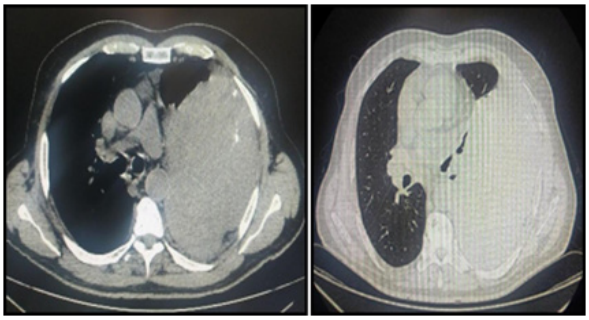
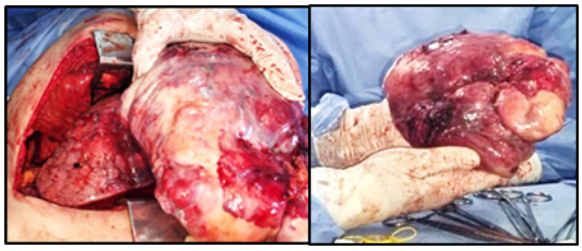


Figure 3. Vue per opératoire de la tumeur. La pièce opératoire mesure 20 cm de longueur et 6 kg de poids.



Discussion

Les tumeurs fibreuses solitaires de la plèvre (TFSP) sont des tumeurs mésenchymateuses d'évolution lente, extrêmement rares et représentent moins de 5% de toutes les tumeurs pleurales. Environ 800 cas ont été rapportés dans la littérature.

La majorité des TFSP sont pédiculées avec des caractéristiques histologiques bénignes [2].Les formes indifférenciées ou « fibrosarcome pleural »existent, de même que la transformation d'une TFSP bénigne en une tumeur maligne. C'est pourquoi la résection complète de toutes les TFSP est obligatoire [3, 4]. Certaines formes se propagent localement et peuvent atteindre la région axillaire, le creux sus-claviculaire et la paroi thoracique. Les métastases ganglionnaires hilaires et médiastinales surviennent chez moins de 50% des patients [5]. Notre patient avait des adénopathies en peropératoire mais réactionnelles, non métastatiques à l'étude anatomopathologique.

Le diagnostic préopératoire est parfois difficile en raison de la rareté de ces tumeurs et de l'absence de signes radiologiques spécifiques [6]. La tumeur est radiologiquement similaire aux autres tumeurs des tissus mous. Elle peut contenir des zones kystiques, des calcifications ou des zones hémorragiques. La taille peut varier de 1 à 40 cm. Les TFSP prennent naissance de la plèvre viscérale dans les deux tiers des cas et sont fréquemment pédiculées.

Le pédicule contenant généralement de gros vaisseaux nourriciers avec parfois une attache pulmonaire. Dans les autres cas elles naissent de la plèvre pariétale avec une large base d'implantation. Une distinction radiologique importante pour faciliter la délimitation d'une tumeur pleurale par rapport à une tumeur pulmonaire parenchymateuse est l'angle que forme la tumeur avec la paroi thoracique, qui est obtus pour une tumeur pleurale et aigu pour les tumeurs du poumon [7].

Dans notre observation le diagnostic préopératoire a pu être obtenu par une biopsie transthoracique dont les études histologiques et immuno-histochimiques ont conclu à une tumeur fibreuse solitaire. L'exploration peropératoire a révélé une masse tumorale comblant la cavité thoracique, d'une taille de plus de 20 cm sur son grand axe provenant de la plèvre viscérale, comme fréquemment rapporté dans la littérature [5].

Le challenge était la possibilité de réaliser une exérèse complète de la tumeur. Toutefois, la mobilisation de cette masse était sans difficulté après un agrandissement de la thoracotomie, à cause de l'absence d'adhérences intimes avec la paroi, le diaphragme et le médiastin. Le poumon gauche était affaissé et ne présentait pas une adhérence importante avec la masse.

La résection chirurgicale complète est le traitement de référence et le facteur pronostique le plus important. Le choix de l'approche chirurgicale (chirurgie thoracoscopique vidéo-assistée ou thoracotomie standard) repose essentiellement sur la taille de la tumeur, la difficulté d'exérèse et l'expertise de l'équipe chirurgicale [8].

Dans certains cas, une exérèse pulmonaire ou de la paroi thoracique, voire d'une partie du diaphragme associée à la résection tumorale, est nécessaire. Dans une série de 84 patients opérés pour TFSP à la Mayo Clinic (Rochester,-Minnesota, USA), l'exérèse pulmonaire était pratiquée chez près des trois quarts des patients, et une résection de la paroi thoracique a été nécessaire chez 3 patients. l'évolution était marquée par la régression de l'ensemble des signes cliniques.

L'approche opératoire et l'étendue de l'excision chirurgicale étaient dictées par la taille et la topographie de la TFSP [9]. Dans notre cas une thoracotomie postéro latérale était incontournable du fait de l'important volume de la tumeur (qui pesait six kg) ainsi que ses rapports étroits avec la paroi thoracique et le poumon gauche. L'exérèse de la tumeur était complète sans avoir recours à une exérèse pulmonaire associée.

A 2 ans de recul, aucun signe de récidive locale n'est observé. En général, après une résection chirurgicale complète, on peut espérer une longue survie dans presque tous les cas. Cependant, l'exploration préopératoire et la prise en charge des TFSP malignes restent des questions complexes du fait de la difficulté diagnostique et thérapeutique [10].

Conclusion

Cette observation met en évidence une rare tumeur fibreuse solitaire géante de la plèvre, présentant des caractéristiques bénignes. Le défi est la réalisation d'une exérèse complète, seule garant d'un bon pronostic et de la nette réduction du risque de récidive locale. Un suivi postopératoire est de fait car l'évolution de la tumeur est imprévisible et mal définie.

Conflits d'intérêt

Les auteurs ne déclarent aucun conflit d'intérêts.

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La présentation et la longueur maximale du manuscrit (page de titre, résumé, références, tableaux et figures non compris) diffèrent selon le type d'article :

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Le corps de l'article comprend :

- L'Introduction est courte, justifie le travail et en expose la problématique et les objectifs, en rappelant brièvement les données de la littérature.

- Dans Méthodes, les critères de sélection de la population d'étude, ainsi que les compositions de groupes etc. sont clairement indiqués; la méthodologie statistique est présentée. Ce chapitre ne fournit aucun résultat. Il se termine par l'exposé des tests statistiques.

- Dans Résultats : En fonction de leur nombre ou de leur type, les résultats sont donnés sous forme d'effectifs et de pourcentages, de moyenne (avec l'écart-type ou l'intervalle de confiance), de médiane (avec les extrêmes), de probabilité (avec si possible l'intervalle de confiance). Les longues énumérations de chiffres dans le texte doivent être évitées: il faut leur préférer un ou plusieurs tableau(x) ou figure(s)..

- Discussion : Ce chapitre commente les résultats, sans en donner de nouveaux ni les répéter, et les confronte à ceux publiés dans la littérature. Il commence par un bref résumé des résultats. - Revue systématique (5.000 mots, 80 références au maximum, résumé en français et en anglais). Cette section regroupe des articles de fond faisant un point approfondi des développements récents d'un sujet, question d'actualité ou nouveau progrès, à partir d'une analyse critique des données de la littérature et des controverses qui peuvent y être associées. Il s'agit donc de proposer une synthèse critique des travaux publiés sur un thème donné, débouchant sur des propositions utiles et constructives.

- Mise au point : (2.500 mots, 50 références au maximum, résumé en français et en anglais). Les mises au point traitent en profondeur les développements récents sur un sujet choisi. A part quelques références essentielles, la littérature analysée est celle des cinq dernières années. Les mises au point obéissent aux mêmes instructions générales que celles concernant les revues systématiques, dont elles diffèrent par leur caractère moins exhaustif.

- Cas clinique et brève communication (1.000 à 1.500 mots, 10 références au maximum, résumé en français et en anglais). Après une éventuelle introduction brève (quelques lignes), la rédaction du cas clinique doit être structurée en 2 parties:

• L'observation doit être rapportée brièvement;

• La discussion a pour but de commenter le cas. Cette discussion doit donc être relativement courte et ne pas dépasser la moitié de l'article. Le paragraphe se termine sur les perspectives ouvertes par cette observation.

- Notes méthodologiques (1.500 mots, 30 références au maximum). Cette rubrique s'adresse aux thésards (à partir de la 2ème inscription). Elle accueille des textes courts présentant les méthodologies des travaux des doctorants. Les articles doivent comporter un résumé struc-

turé et inclure :

-une « Introduction », qui fait le point sur l'état des connaissances et la justification de l'étude ; -une section « Méthodes », qui décrit la population étudiée, les méthodes utilisées, et le plan statistique ; -une section « retombées de l'étude », qui discutent les différentes possibilités et les perspectives qu'elles ouvrent.

- Lu pour vous : (500 mots, 3 références) sont des articles courts de commentaire ou d'analyse critique d'un ouvrage, chapitre d'ouvrage ou article important publié dans la littérature nationale ou internationale, dans le champ de la santé. Un article de « Lu pour vous » doit comporter le titre, les auteurs et les références de l'article original. Ces articles de veille scientifique ne sont pas soumis à révisions. Ils doivent être signés par l'auteur qui engage sa responsabilité.

- Lettres à la rédaction (500 mots, 5 références, pas de résumé). Les lettres à la rédaction sont à différencier de la correspondance. Signées par cinq auteurs maximum, elles peuvent porter sur les résultats préliminaires d'une étude, une information scientifique ou professionnelle. Elles peuvent aussi aborder des sujets d'actualité.

3.2. RESUMES ET MOTS CLES

Chaque article, hormis les Editoriaux et lettre à la rédaction, doit comporter un résumé en français et en anglais, sans abréviation ni référence, de 300 mots au maximum. Les résumés sont structurés de la façon suivante : Objectifs; Méthodes; Résultats ; Conclusions. Les mots clés (en français et en anglais), au nombre de 3 à 5, doivent être pertinents et descriptifs.

3.3. TEXTE

Le texte est rédigé dans un style clair, concis et précis. Dans le corps du texte, chaque référence est suivie d'une numérotation en chiffre arabe entourée de crochets (par exemple : [1]). La référence peut être citée plusieurs fois dans le texte dans ce cas, elle garde la même numérotation. Le corps du texte est suivi des remerciements éventuels, conflits d'intérêt, références, tableaux, et enfin les légendes des figures.

3.4. TABLEAUX

Chaque tableau doit être présenté sur un fichier word séparé, numéroté en chiffres arabes et indexé dans le texte par appel (par ordre d'apparition) de son numéro entre parenthèses. Il est accompagné d'un titre (placé au-dessus) et, éventuellement, de notes explicatives (audessous). Quatre tableaux sont acceptés au maximum.

3.5. FIGURES

Les figures sont jointes dans des fichiers séparés. Les légendes doivent être fournies à part indiquant clairement l'objet de la figure et précisant les abréviations. Pour permettre à l'éditeur d'identifier facilement les figures transmises, il est recommandé de nommer les fichiers en indiquant le numéro de la figure et le format utilisé. Par exemple : « fig1.tif », pour le fichier de la figure 1 sous format TIFF. Quatre figures sont acceptées au maximum.

3.6. REFERENCES BIBLIOGRAPHIQUES

Les références sont présentées conformément aux normes de Vancouver (International Commitee of Medical Journal Editors http://www.icmje.org/).

Article de périodique classique.

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4. Déclaration des conflits d'intérêt

Les auteurs doivent signaler tout lien d'intérêts que pourrait susciter leur travail de manière générale en suivant les recommandations ci-après citées : un lien d'intérêts existe quand un auteur et/ou un coauteur a des relations financières ou personnelles avec d'autres personnes ou organisations qui sont susceptibles d'influencer ses jugements professionnels concernant une valeur essentielle (bien du patient, intégrité de la recherche...).

5- Plagiat

Un contrôle par un logiciel anti-plagiat est systématiquement effectué pour toute soumission. Tout plagiat entraine le rejet de l'article et la non-considération de toute soumission ultérieure provenant de l'auteur.

6. Décision du comité de rédaction

6.1. Acceptation du manuscrit Un avis d'acceptation du manuscrit est adressé lorsque la rédaction a considéré cette acceptation, après avis des reviewers. Les auteurs pourront encore se voir réclamer des modifications de forme et/ou de fond, parfois nécessaires pour la préparation des épreuves de leur article. Le fait de demander des modifications majeures ne signifie pas que l'article est accepté. Les versions corrigées des articles doivent respecter les indications suivantes :

• être accompagnées d'une lettre reprenant chacune des modifications demandées dans les commentaires de lecture, et qui précise : - soit la modification effectivement apportée au texte par l'auteur ; - soit la raison pour laquelle celui-ci n'a pas souhaité apporter la modification demandée, ou n'a pas été en mesure de le faire.

• sur la version corrigée elle-même, la modification apportée doit être signalée (au moyen de soulignements, surlignages, caractères en couleur, etc.)

6.2. Refus du manuscrit Le Comité de Rédaction se réserve le droit de refuser les manuscrits qui s'éloignent des instructions précédemment citées et en avisera l'auteur correspondant.

6.3. Corrections d'épreuves Les épreuves seront envoyées à l'auteur par courrier électronique (format pdf) après acceptation définitive de l'article. Seules les fautes typographiques pourront être corrigées. Aucun additif ne pourra être fait par rapport au manuscrit accepté définitivement. Les auteurs feront le nécessaire pour que ces épreuves soient retournées à l'éditeur revêtues de la mention « Bon à tirer » dans les 72 heures suivant leur réception. En cas de retard, l'éditeur se réserve le droit de procéder à l'impression, après accord de la rédaction.

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