

THE UTILITY OF USUAL SERUM TESTS FOR THE PROGNOSIS OF PATIENTS WITH CUTANEOUS METASTASES

Diana BODOARCA^{1,2}✉, Oana M. PATRASCU^{2,3}✉, Camelia C. DIACONU^{1,2}, Samuel BODOARCA⁴, Mariana COSTACHE^{2,3}

¹ Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Bucharest, Romania

² “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

³ Department of Pathology, University Emergency Hospital, Bucharest, Romania

⁴ “Marius Nasta” National Pneumophthisiology Institute, Bucharest, Romania

Received 09 Jan 2022, Accepted 14 Febr 2022

<https://doi.org/10.31688/ABMU.2022.57.1.06>

ABSTRACT

Introduction. Cutaneous metastases are usually observed in end-stage cancers. In some cases, the diagnosis of skin metastases is not clinically evident. New studies have found that serological markers, such as fibrinogen and lactate dehydrogenase (LDH), represent predictive factors of cutaneous metastases and could be used in the follow-up.

The objective of our study was to evaluate these two markers (fibrinogen and LDH) and to find if there are any correlation between different parameters such as patients' age, dimensions, and type of the tumour, as well as local complications.

Materials and methods. We conducted a retrospective study on 56 patients with cutaneous metastases. We analysed different parameters of patients who underwent skin biopsies or surgical excision, such as age,

RÉSUMÉ

L'utilité des tests sériques habituels pour le pronostic des patients présentant des métastases cutanées

Introduction. Les métastases cutanées sont généralement observées dans les cancers en phase terminale. Dans certains cas, le diagnostic de métastases cutanées n'est pas cliniquement évident. De nouvelles études ont montré que les marqueurs sérologiques, tels que le fibrinogène et la lactate déshydrogénase (LDH), représentent des facteurs prédictifs de métastases cutanées et pourraient être utilisés dans le suivi.

L'objectif de notre étude était d'évaluer ces deux marqueurs (fibrinogène et LDH) et de rechercher s'il existe une corrélation entre différents paramètres tels que l'âge des patients, les dimensions et le type de tumeur, ainsi que les complications locales.

✉ Address for correspondence:

Oana M. PATRASCU

Address: Department of Pathology, University Emergency Hospital, Splaiul
Independentei Str. No. 169, 010271 Bucharest, Romania

Email: oanamaria.patrascu@gmail.com

Diana BODOARCA

Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Calea
Floreasca no.8, Bucharest 14461, Romania

Email: diana.belciu@yahoo.com

number, diameter, localization or complications, type of primary neoplasia, other internal organ malignancies, as well as serological levels of LDH and fibrinogen.

Results. The study included patients with various types of malignant tumours, most of them with melanoma, followed by different types of adenocarcinomas and leiomyosarcoma. Our cohort also included some rare cases of uterine cervix adenocarcinoma metastases, renal cell metastases and pancreatic metastases. Regarding the serological markers, we identified that fibrinogen correlates with the diameter of the skin nodules, LDH correlates with the age of the patients diagnosed with melanoma, and the two serological parameters correlate with one another.

Conclusions. Fibrinogen and LDH can be considered poor prognostic factors for patients with melanoma metastases. As the two markers correlate with one another and with some of the analysed parameters, they could, in the future, be useful to better estimate the malignant disease outcome.

Keywords: skin metastasis, cutaneous tumours, biomarkers, fibrinogen, LDH.

List of abbreviations

AJCC – American Joint Committee on Cancer

CDX2 – caudal type homeobox 2

HE – hematoxylin–eosin

IHC – immunohistochemistry

kDa – kilodalton

LDH – lactate dehydrogenase

NHL – non-Hodgkin lymphoma

NOS – not otherwise specified

SCC – squamous cell carcinoma

INTRODUCTION

Many studies have found that different serological markers, like fibrinogen and lactate dehydrogenase (LDH), can be considered prognostic factors for disease outcome and overall survival in metastatic disease, especially in pretreated end-stage cancers and those with first-line treatments^{1,2}. Fibrinogen is a glycoprotein synthesized by hepatocytes, with roles in acute phase inflammation¹, and in tumour progression and metastasis development in different types of cancers, such as breast, lung, gastric, pancreatic, hepatocellular carcinomas, as well as in cutaneous squamous cell carcinoma and melanoma^{2,4}. Fibrinogen-related products are considered to have an important role in blood coagulation, tumour stroma formation and in hemostatic complications, especially in end-stage tumours, promoting migration

Matériels et méthodes. Nous avons mené une étude rétrospective sur 56 patients présentant des métastases cutanées. Nous avons analysé différents paramètres des patients ayant subi des biopsies cutanées ou une excision chirurgicale, tels que l'âge, le nombre, le diamètre, la localisation ou les complications, le type de néoplasie primaire, d'autres tumeurs malignes des organes internes, ainsi que les taux sérologiques de LDH et de fibrinogène.

Résultats. L'étude a inclus des patients atteints de différents types de tumeurs malignes, la plupart d'entre eux avec un mélanome, suivi de différents types d'adénocarcinomes et de léiomyosarcomes. Notre cohorte comprenait également quelques rares cas de métastases d'adénocarcinome du col de l'utérus, de métastases des cellules rénales et de métastases pancréatiques. Concernant les marqueurs sérologiques, nous avons identifié que le fibrinogène est corrélé au diamètre des nodules cutanés, la LDH est corrélée à l'âge des patients diagnostiqués avec un mélanome, et les deux paramètres sérologiques sont corrélés entre eux.

Conclusions. Le fibrinogène et la LDH peuvent être considérés comme des facteurs de mauvais pronostic pour les patients présentant des métastases de mélanome. Comme les deux marqueurs sont corrélés entre eux et avec certains des paramètres analysés, ils pourraient, à l'avenir, être utiles pour mieux estimer l'évolution de la maladie maligne.

Mots-clés: métastases cutanées, tumeurs cutanées, biomarqueurs, fibrinogène, LDH

of different types of cells, wound repair mechanisms and neovascularization⁵. High levels of fibrinogen are known for their role as predictors in cardiovascular and chronic kidney disease⁶.

Lactate dehydrogenase (LDH) is a well-known serum marker for cutaneous metastatic melanoma and was included in the staging guideline since the 2009 American Joint Committee on Cancer (AJCC) Staging Manual⁷. LDH is important in the processes of glycolysis, the preferred mechanism of glucose metabolism of the tumour cells¹.

The prognostic role of LDH was studied for melanoma, but also for non-Hodgkin's lymphoma, nasopharyngeal and breast carcinomas¹.

Cutaneous metastases are relatively uncommon, with an incidence ranging from 0.6 to 10% of all patients with malignancies⁸. The most common tumours leading to skin metastases are melanomas,

both in men and in women, followed by breast carcinomas in women and lung carcinomas in men^{9,10}. Colorectal carcinomas can also frequently complicate with skin metastases.

THE OBJECTIVE OF OUR STUDY was to analyse and characterize various types of cutaneous metastases and to highlight any possible correlations between different prognostic factors, such as patients' age, tumours' dimensions, fibrinogen and LDH levels, for a better understanding and prediction of the disease outcome.

MATERIALS AND METHODS

Fifty-six cases of cutaneous metastases were analysed. We collected data regarding the patients' age, number and location of the metastases, diameters of the skin nodules, complications such as infection, ulceration, hemorrhage, and necrosis, and data about the tumour's origin, type of neoplasia, existence of other metastases, malignancies, or associated diseases, as well as serum levels of fibrinogen and LDH.

All tumours were diagnosed in the Pathology Department of the University Emergency Hospital of Bucharest, Romania. The tissue samples were fixed with 10% buffered formalin and were processed by conventional histopathological method, using inclusion in paraffin and hematoxylin-eosin (HE) staining. Some of the cases were further analysed with immunohistochemical stains in other medical centres.

All the procedures and experiments of this study were in accordance with the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. The study was approved by the Ethics Committee of the University Emergency Hospital of Bucharest, Romania (approval no. 31673/01.07.2020). Written informed consent was obtained from all the patients included in the study.

Microsoft Excel for Data Analysis for descriptive statistics and regression coefficient for any presumable correlations were used, with a statistically significant p-value less than 0.05.

RESULTS

The mean age of the patients was 63.57 ± 14.73 years. 33 (57%) patients were women. The diameters of the analysed tumours ranged from 6 mm to 50 mm, with a mean value of 24.37 ± 13.24 mm. 29 patients presented a single metastasis and 33 patients had multiple visceral and lymph node metastases. Half of the analysed cases (29 patients) presented local complications, such as necrosis, hemorrhage, ulceration, or infection.

Out of 56 cases, 28 patients were diagnosed with epithelial carcinomas¹¹, such as carcinomas or adenocarcinomas, 27 patients with melanoma (Fig. 1) and one with leiomyosarcoma. One patient was suspected of a neuroendocrine carcinoma or a multiple myeloma, needing further immunohistochemical (IHC) investigations.

The distribution of the primary tumour according to the histological type in women is presented

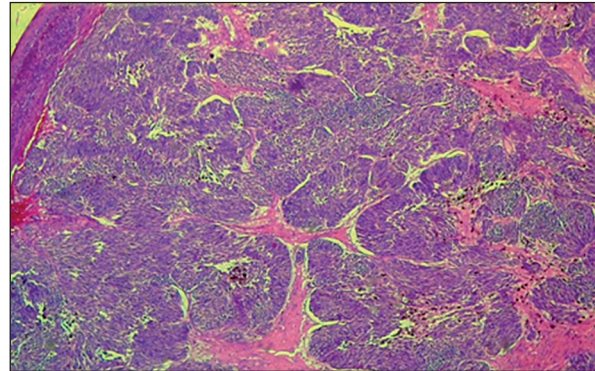


Figure 1. Light microscopy of melanoma metastases localized in the skin dermis, without any epidermal or junctional involvement. The tumour is composed of fusiform cells with marked pleomorphism, high mitotic rate and moderate but disorganized pigmentation. HE stain, 40x.

in Table 1. Out of the 33 women patients, 13 were diagnosed with melanoma, 10 with breast carcinoma, two with serous ovarian carcinoma, two with gastric carcinoma, two with pancreatic adenocarcinoma, one with uterine cervix squamous cell carcinoma, one with uterine cervix adenocarcinoma, one with colonic adenocarcinoma, and one had leiomyosarcoma.

Of the 23 male patients, 14 had melanoma, 4 were diagnosed with colorectal adenocarcinoma, two were diagnosed with renal tumours, one patient presented with pulmonary squamous cell carcinoma (SCC), one with cutaneous SCC and one with unknown primary tumour, necessitating IHC.

The distribution of the primary tumour according to the histological type in men is presented in Table 2.

A total of eight patients were diagnosed with cutaneous metastatic adenocarcinoma. Five patients (71%) were known with colorectal neoplasia (two of mucinous type, two of NOS type and one with unspecified histological subtype) (Fig. 2, 3), two with pancreatic adenocarcinoma (NOS and clear cell subtype), and one with uterine cervix adenocarcinoma NOS type. The uterine cervix adenocarcinoma metastasis was diagnosed in a 63-year-old patient and

Table 1. The distribution of primary tumours according to the histological type in women

Women	Uterin Cervix	Colon	Cutaneous	Gastric	Breast	Muscular	Ovarian	Pancreatic
Adenocarcinoma	1	1						2
Mucinous		1						
Not otherwise specified (NOS)	1							1
Clear cell								1
Carcinoma				2	9		2	
Ductal					6			
Lobular					2			
NOS				1	1			
Serous							2	
Unknown				1				
Leiomyosarcoma						1		
Melanoma			13					
Unknown			7					
Acral			1					
Superficial spreading			1					
Nodular			2					
Polypoid			2					
SCC	1				1			
Nonkeratinized	1				1			

NOS- Not otherwise specified
 SCC - Squamous Cell Carcinoma

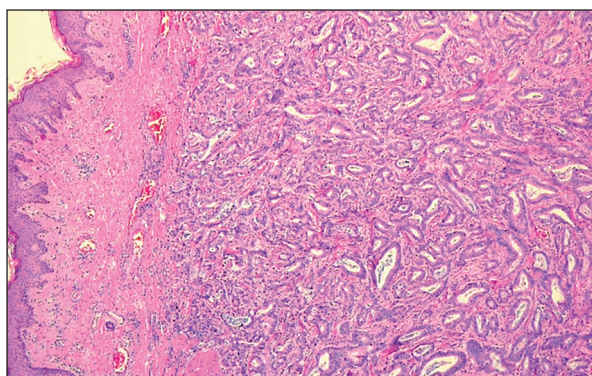


Figure 2. Histological microscopy image of malignant proliferation composed of infiltrative cribriform structures suggesting an adenocarcinoma metastasis in the skin, HE 40x.

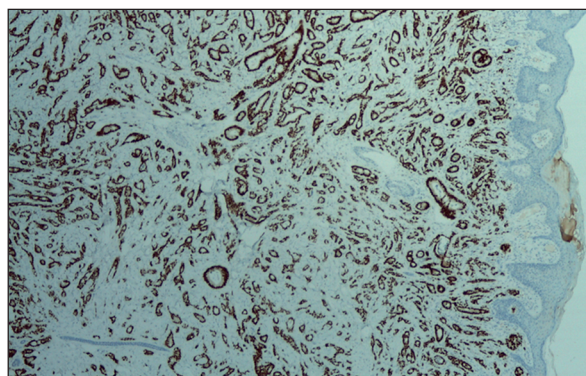


Figure 3. Immunohistochemical CDX2 (caudal type homeobox 2) staining of a colorectal skin metastasis, 40x.

presented as a single nodular tumour of 10 mm diameter localized near the umbilicus.

The metastases' grade of differentiation ranged from well to poorly differentiated. The average age of patients with adenocarcinoma was 64.16 years, and the average dimension of the metastatic nodules was 22.93 mm. The serum levels of fibrinogen ranged from 163 mg/dL to 696 ml/dL, with an average value of 416.73 mg/dL. There were correlations between patients' age and fibrinogen levels, and we determined a weak

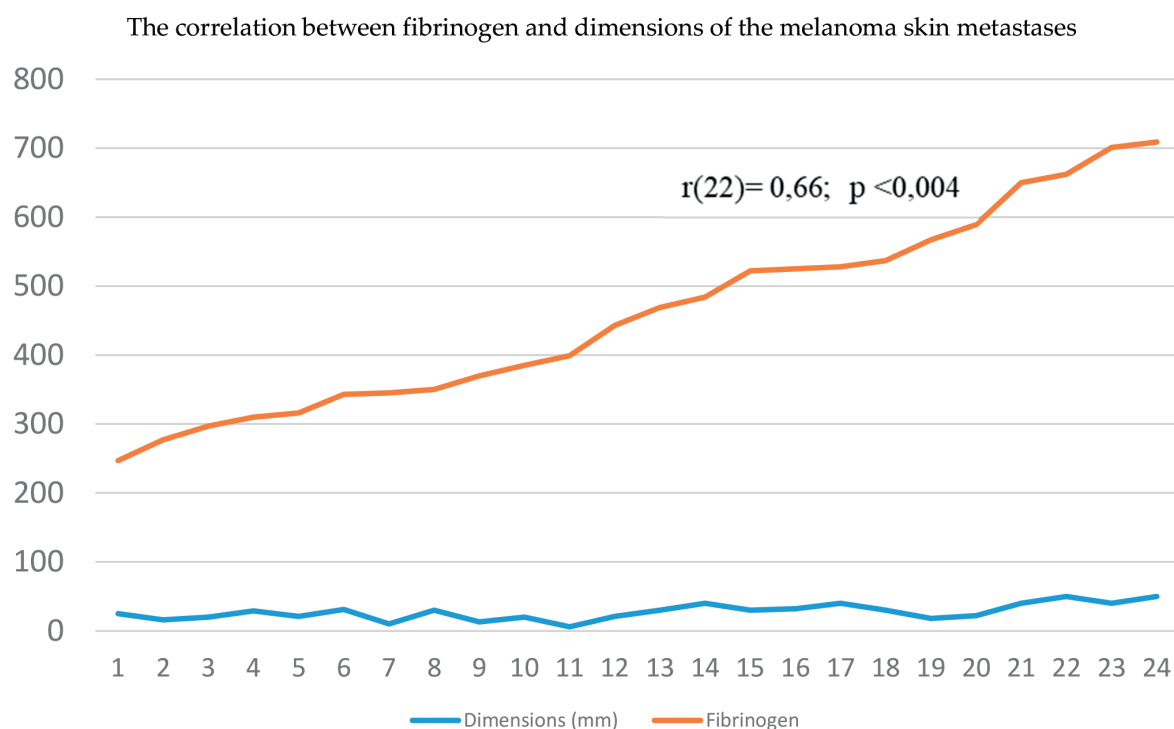
correlation between serum fibrinogen levels and dimensions of metastatic nodules ($r(7) = 0.36, p = 0.03$).

The distribution of cutaneous metastatic carcinomas according to the primary tumour was: from the 19 patients with carcinomas, 10 had breast cancers (6 with ductal type carcinoma, two with lobular carcinomas, one considered of NOS type and one as squamous cell carcinoma with breast origin), two had ovarian serous carcinoma, two had tubular and tubulo-cystic renal tumours, two had gastric carcinoma

Table 2. The distribution of the primary tumours according to the histological type in men

Men	colon	colorectal	cutaneous	pulmonary	rectal	renal	unknown
Adenocarcinoma	2	1			1		
Unknown	1						
Not otherwise specified	1	1					
Mucinous					1		
Carcinoma						2	
Tubular						1	
Tubulo-cystic						1	
Neuroendocrine carcinoma/ myeloma							1
-							1
Melanoma			14				
Acral			4				
Superficial spreading			1				
Nodular			7				
Unknown			2				
SCC			1	1			
-				1			
Nonkeratinized			1				

SCC - Squamous Cell Carcinoma

**Figure 4.** The correlation between fibrinogen and dimensions of the melanoma skin metastases.

and there was only one case of SCC of cutaneous, pulmonary and uterine cervix origin.

The average age of all these patients was 63.57 years. The average dimension of the metastases was 24.42 mm, and the average fibrinogen level was

434.51 mg/dL. Of all 56 patients, 27 patients had multiple cutaneous metastases, and 33 patients had visceral, osseous, retroperitoneal or lymph node metastases. 29 cases presented with local tumour complications, such as ulcerations, necrosis, or hemorrhage.

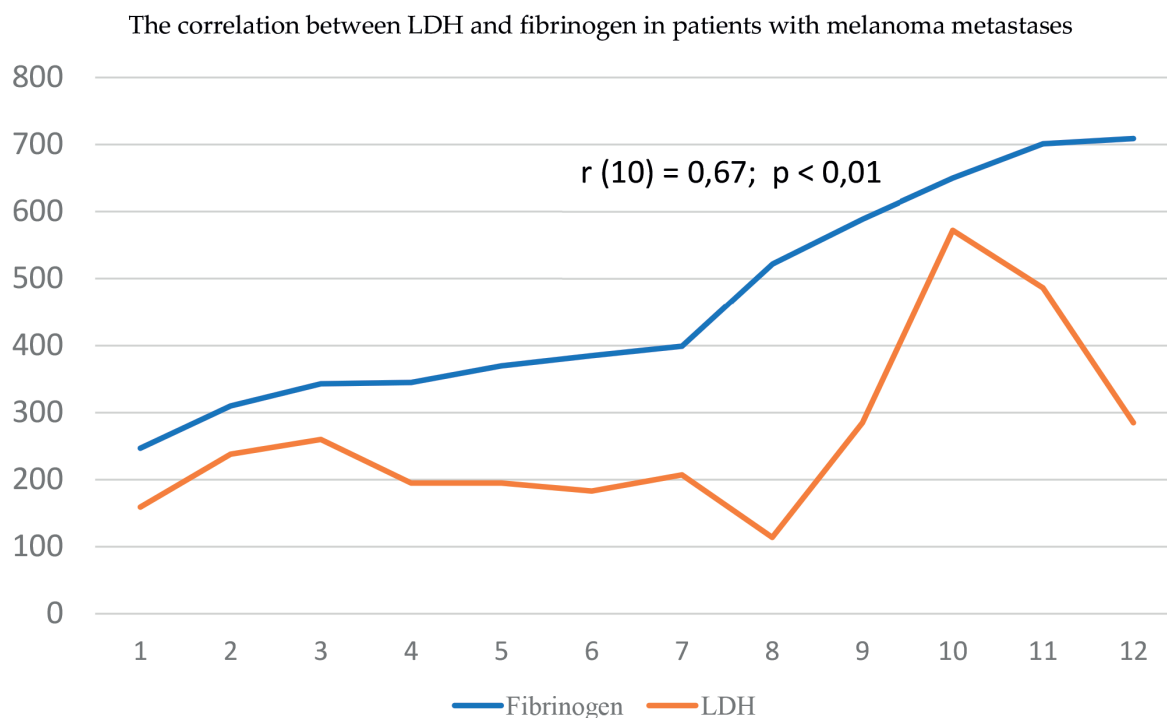


Figure 5. The identified correlation between LDH and fibrinogen in patients with melanoma metastases.

The correlation between high levels of LDH and the age of the patients with melanoma skin metastases

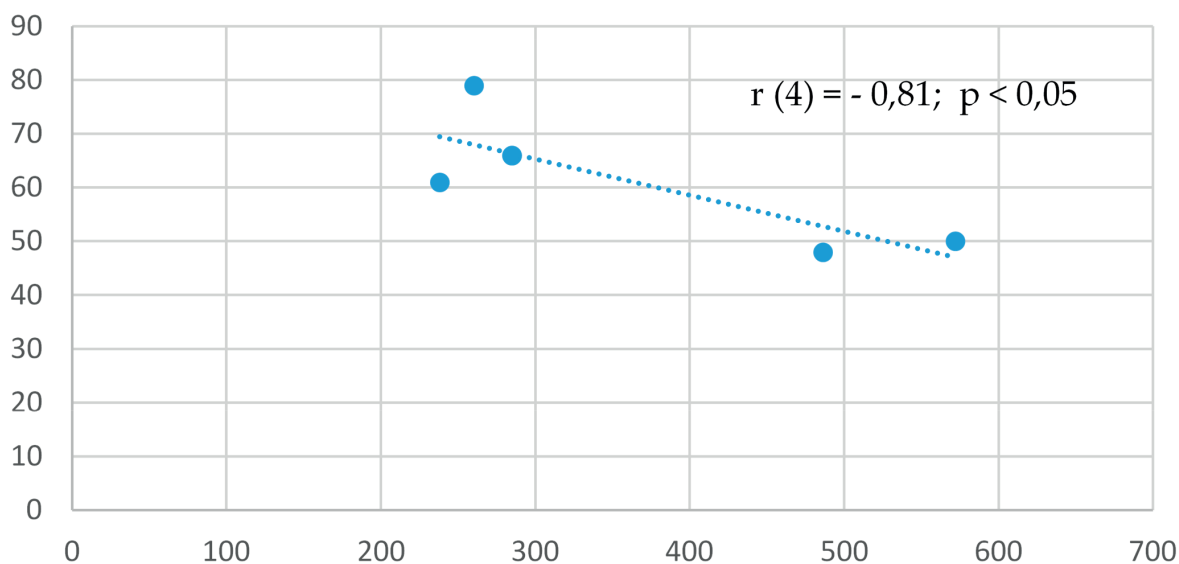


Figure 6. The correlation between high levels of LDH and the age of the patients with melanoma skin metastases.

The most common localization of cutaneous metastases was the abdominal area. Breast carcinomas frequently metastasized on the anterior thorax (5 cases), 3 patients had cutaneous metastases on the extremities (axilla) and 2 cases metastasized on the scalp.

Of all patients with melanoma's cutaneous metastases, 53% were males. 17 (males and females) had multiple cutaneous metastases and 14 presented with lymph node, osseous and pulmonary metastases. One patient had also salivary gland metastasis. The average

age of the patients with melanoma metastases was 62.11 years, and the average nodule diameter was 29 mm.

The average level of fibrinogen in melanoma patients was 459 mg/dL (in 24 cases), and the average LDH level was 251.71 IU/L. There were no correlations between the patients' age and the dimensions of the metastatic nodules or between the age and fibrinogen values. We found, however, a moderate correlation between the levels of fibrinogen (high and normal) and the diameters of the metastases ($r(22) = 0.66$, $p < 0.004$) (Fig. 4), but no significant correlation between LDH and the metastatic nodules' dimensions. Interestingly, we identified a moderate correlation between fibrinogen and LDH levels ($r(10) = 0.67$, $p = 0.01$), including patients with only high levels of the two serum markers (Fig. 5).

Moreover, we identified a strong negative correlation (Fig. 6) between the age of the melanoma patients and the high levels of LDH ($r(4) = -0.81$, $p < 0.04$), although the cohort examined included a small number of patients. Only eight patients from this study had elevated levels of LDH, of which five had melanoma metastases.

For non-melanoma patients, no correlation could be highlighted between the levels of LDH and fibrinogen, nor between the two parameters and age or diameters of metastatic nodules. As revealed also by other studies, the results of our study sustain that the high levels of fibrinogen could be considered an indicator of a poor prognosis, with metastatic potential, at least in melanoma patients.

DISCUSSION

Cutaneous metastases are uncommon findings in oncological patients, their incidence ranging between 0.5 and 10%⁸. The most frequent cancer metastasizing in the skin is melanoma, both in men and women, followed by breast, colorectal and lung carcinomas⁹⁻¹³. In our study, almost half of the examined metastases were of melanoma, both in men and women, data consistent with the literature. Furthermore, the second most frequent type of metastases diagnosed in female patients were from breast carcinomas, followed by gynecological tumours, gastric and pancreatic cancers. For men, the second most common diagnosed tumour was colorectal cancer, followed by renal tumours.

Interestingly, although uterine cervical tumours are known to rarely metastasize in the skin⁸, we identified two cases of cervix tumours, one adenocarcinoma and one SCC. The adenocarcinoma metastasis was located near the umbilicus, while the cervical SCC metastasized to the anterior thorax. Moreover, our group of study included two cases of renal

carcinomas metastasized to the skin. These tumours are difficult to diagnose as skin metastases, because of their similarity to other cutaneous pathologies. Other two rare cases of pancreatic adenocarcinomas metastasizing in the skin were identified. Pancreatic carcinomas rarely metastasize onto the skin^{12,14,15}, the umbilicus being the most frequent location, as observed in our study.

The mean age did not vary considerably between males and females, nor between the subcategorized groups. Half of the analysed metastases presented at least one complication.

Clinically, there is a wide variety of presentations of cutaneous metastases, from inflammatory aspects to nodules or cystic masses. They can mimic almost any skin pathology, being considered by some authors "great imitators"^{9,16}. Histologically, they are frequently similar like the primary tumour, although a great number of cases can be classified as poorly or undifferentiated in comparison to primary tumours¹⁷. A careful examination will reveal, most of the time, the diagnostic criteria. Moreover, most of the patients are known with a primary cancer. Nonetheless, immunohistochemistry remains mandatory for a positive diagnosis and for differential diagnosis. We also had two cases in whom a clear and final diagnosis couldn't be established without further IHC examination. One case raised the suspicion of a neuroendocrine carcinoma or multiple myeloma, and one case raised differential diagnosis problems between melanoma and leiomyosarcoma.

In our study, most melanoma metastases appeared on extremities, followed by thorax and abdomen, while breast carcinomas frequently metastasized on the anterior thorax, data consistent with the literature¹⁸.

We also analysed the serum levels of fibrinogen and LDH in the group of study. Fibrinogen is a 340 kDa glycoprotein synthesized by hepatocytes, fibroblasts and some epithelial and tumoral cells, involved in clot forming, acute phase inflammation and wound healing^{3,19}. Moreover, high levels of fibrinogen are linked to cardiovascular diseases and chronic kidney disease⁶. Many tissues synthesize fibrinogen in inflammatory conditions, which further determines an inflammatory microenvironment for various tumours. Studies have showed that the levels of fibrinogen are also linked with tumour dissemination and size, metastatic potential, and tumour progression⁶, as well as with tumour progression, staging, metastases, and overall survival^{2,6,19,20}. Fibrinogen increases the metastatic potential of circulating cells, sustaining adherence and survival of tumour cells in the newly formed vascularization, although it seems that it doesn't impact the growth of existing metastases⁵. High levels of

fibrinogen were observed in various neoplasia, including lung carcinomas²⁰, gastric, hepatic, or gynecological tumours^{2,6,19}. In our study, we found a statistically significant correlation between the levels of fibrinogen (high and normal) and the size of metastatic nodules in melanoma patients. The group of patients with melanoma was the most relevant, because the number of cases was higher comparative with non-melanoma patients. One study emphasized the role of fibrinogen as a predictive factor in patients with diagnosed melanoma⁴. LDH is an acknowledged prognostic marker for melanoma, both during pre- and post-treatment⁷. High levels of LDH are correlated with a poor outcome in melanoma patients^{7,21}, and in those with breast and nasopharyngeal carcinomas^{1,22}. The mechanism behind LDH elevation in different types of cancers is explained by glycolysis pathway, namely by the Warburg effect¹. LDH converts pyruvate in lactate in the process of glycolysis, enhancing, thus, the anaerobic metabolism of the tumour cells¹, but it also maintains an inflammatory microenvironment, promotes angiogenesis, cell migration and metastasizing²². In our study, LDH correlated with the patients' age, as well as with fibrinogen levels, suggesting that LDH could be considered an indicator of a poor prognosis. The limitations of the study are related to the small sample size and its retrospective type.

CONCLUSIONS

Fibrinogen and LDH are two serological markers easy to measure in current medical practice. Fibrinogen and LDH levels correlate with each other and with others prognostic markers, such as patients' age or dimensions of the metastatic nodules in patients with melanoma. There is a need for bigger studies to evaluate the interactions between malignant tumour cells and usual serological markers.

Author Contributions:

D.B., O.M.P. and M.C. contributed substantially to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and were involved in the drafting of the manuscript. C.C.D. and S.B. contributed substantially to the analysis and interpretation of the data and were involved in the drafting of the manuscript. C.C.D. and M.C. were involved in the critical revisions of the manuscript for important intellectual content. D.B. and O.M.P. were responsible for confirming the authenticity of all raw data. All authors have read and approved the final manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study. The study was approved by the Ethics Committee of the University Emergency Hospital of Bucharest, Romania (approval no. 31673/ 01.07.2020). Written informed consent was obtained from all the patients included in the study".

"No funding for this study"

Acknowledgements:

None

REFERENCES

1. Long G, Tang W, Fu X, et al. Pre-treatment serum lactate dehydrogenase predicts distant metastasis and poor survival in nasopharyngeal carcinoma. *Journal of Cancer* 2019;10(16):3657-3664.
2. Zhang X, Long Q. Elevated serum plasma fibrinogen is associated with advanced tumor stage and poor survival in hepatocellular carcinoma patients. *Medicine (Baltimore)*. 2017;96(17):e6694.
3. Salini V, Saggini A, Maccaouro G, Caraffa A, Shalk-Dasthagirisahab YB, Conti P. Inflammatory markers: serum amyloid A, fibrinogen and C-reactive protein - a re-visited study. *European Journal of Inflammation* 2011;9:95-102.
4. Guida M, Ravaioli A, Sileni VC, et al. Fibrinogen: a novel predictor of responsiveness in metastatic melanoma patients treated with bio-chemotherapy: IMI (Italian Melanoma Inter-group) trial. *Journal of Translational Medicine*. 2003;1(1):13.
5. Palumbo JS, Kombrinck KW, Drew AF, et al. Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. *Blood*. 2000;96(10):3302-3309.
6. Yu X, Hu F, Yao Q, et al. Serum fibrinogen levels are positively correlated with advanced tumor stage and poor survival in patients with gastric cancer undergoing gastrectomy: a large cohort retrospective study. *BMC Cancer* 2016;16: 480.
7. Wagner NB, Forschner A, Leiter U, Garbe C, Eigentler TK. S100B and LDH as early prognostic markers for response and overall survival in melanoma patients treated with anti-PD-1 or combined anti-PD-1 plus anti-CTLA-4 antibodies. *British Journal of Cancer*. 2018;119(3):339-346.
8. Nibhoria S, Tiwana KK, Kaur M, Kumar S. A clinicopathological and immunohistochemical correlation in cutaneous metastases from internal malignancies: a five-year study. *Journal of Skin Cancer*. 2014;2014:793937.
9. Wong CY, Helm MA, Kalb RE, Helm TN, Zeitouni NC. The presentation, pathology, and current management strategies of cutaneous metastasis. *North American Journal of Medical Sciences*. 2013;5(9):499-504.
10. Gan EY, Chio MT, Tan WP. A retrospective review of cutaneous metastases at the National Skin Centre Singapore. *The Australasian Journal of Dermatology*. 2015;56(1):1-6.
11. McSweeney WT, Tan K. Cutaneous metastases as a presenting sign of metastatic NSCLC. *Journal of Surgical Case Reports*. 2019;2019(10):rjz279.
12. Zhou HY, Wang XB, Gao F, Bu B, Zhang S, Wang Z. Cutaneous metastasis from pancreatic cancer: A case report

- and systematic review of the literature. *Oncology Letters*. 2014;8(6):2654-2660.
13. Diaconu CC, Arsene D, Paraschiv B, Balaceanu A, Bartos D. Hyponatremic encephalopathy as the initial sign of neuroendocrine small cell carcinoma – case report. *Acta Endocrinologica* 2013;IX(4): 637-642.
 14. Gheorghe G, Bungau S, Ilie M, et al. The early diagnosis of pancreatic cancer: the key for survival. *Diagnostics*. 2020; 10(11):E869. DOI 10.3390/diagnostics10110869
 15. Diaconu C, Mateescu D, Balaceanu A, Marcu M, Jianu V, Stanicã A. Pancreatic cancer presenting with paraneoplastic thrombophlebitis: a case report. *Journal of Medicine and Life* 2010;3(1): 96-99.
 16. Jaros J, Hunt S, Mose E, Lai O, Tsoukas M. Cutaneous metastases: A great imitator. *Clinics in Dermatology*. 2020;38(2):216-222.
 17. Matthiessen LW, Chalmers RL, Sainsbury DC, et al. Management of cutaneous metastases using electrochemotherapy. *Acta Oncologica (Stockholm, Sweden)*. 2011;50(5):621-629.
 18. Teyateeti P, Ungtrakul T. Retrospective review of cutaneous metastasis among 11,418 patients with solid malignancy: A tertiary cancer center experience. *Medicine (Baltimore)*. 2021;100(29):e26737.
 19. Bekos C, Grimm C, Brodowicz T, et al. Prognostic role of plasma fibrinogen in patients with uterine leiomyosarcoma – a multicenter study. *Scientific Reports* 2017;7:14474.
 20. Liu X, Shi B. Progress in research on the role of fibrinogen in lung cancer. *Open Life Sciences*. 2020;15(1):326-330.
 21. Gray MR, Martin del Campo S, Zhang X, et al. Metastatic melanoma: lactate dehydrogenase levels and CT imaging findings of tumor devascularization allow accurate prediction of survival in patients treated with bevacizumab. *Radiology*. 2014;270(2):425-434.
 22. Pelizzari G, Basile D, Zago S, et al. Lactate dehydrogenase (LDH) response to first-line treatment predicts survival in metastatic breast cancer: first clues for a cost-effective and dynamic biomarker. *Cancers (Basel)*. 2019;11(9):1243.