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Factors influencing blood tumor marker concentrations in the absence of neoplasia

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Abstract.
BACKGROUND: Tumor markers (TMs) are a heterogeneous group of molecules used in the diagnosis, prognosis and follow-up of cancer patients. During neoplastic differentiation, cells can either directly synthesize or induce the synthesis of TMs, and the release of these molecules into the bloodstream allows their quantification in biological fluids. Although very small concentrations of TMs are usually present in the serum or plasma of healthy subjects, increased concentrations may also be found in the presence of benign diseases or due to technical interference, producing false positive results.
MATERIAL AND METHODS AND RESULTS: Our review analyses the causes of false positives described between January 1970 to February 2023 for the TMs most frequently used in clinical practice: α-fetoprotein (AFP), β2-microglobulin (β2-M), cancer antigen 15-3 (CA 15-3), cancer antigen CA 19-9 (CA 19-9), cancer antigen CA 72-4 (CA 72-4), cancer antigen 125 (CA 125), carcinoembryonic antigen (CEA), chromogranin A (CgA), choriogonadotropin (hCG), cytokeratin 19 fragment (CYFRA 21-1), neuron-specific enolase (NSE), human epididymis protein 4 (HE4), serum HER2 (sHER2), squamous cell carcinoma antigen (SCCA), protein induced by vitamin K absence-II (PIVKA-II), Pro-gastrin-releasing peptide (Pro-GRP), prostate-specific antigen (PSA), Protein S-100 (S-100) and thyroglobulin (Tg). A total of 247 references were included.
CONCLUSIONS: A better understanding of pathophysiological processes and other conditions that affect the concentration of TMs might improve the interpretation of results and their clinical application.

Keywords: Tumor markers, false positives, benign disease, absence of neoplasia

1. Introduction

Tumor markers (TMs) are a group of molecules (hormones, enzymes, oncoproteins, etc.) with diverse biochemical structures and functions which are directly or indirectly synthesized by the presence of tumors and released into the bloodstream. TMs are useful in several contexts during the management

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of cancer patients, above all in aiding in the diagnosis and monitoring of therapy response. They are normally present in very low concentrations in healthy individuals, but due to technical issues or pathophysiological conditions, their concentrations may be increased in the absence of neoplasia.

When in the absence of neoplasia, the concentration of a TM exceeds the upper reference limit (URL) established for individuals presumed to be healthy, this is considered a false positive. In the main, abnormal values can be attributed to two mechanisms. The first scenario is increased production, given that most TMs are also expressed by normal tissues (e.g. lungs, stomach, intestines, pancreas and skin); inflammation, necrosis or other processes affecting these tissues can stimulate their production and release. Second, their concentration may be increased due to clearance defects, often caused by impaired function of the kidney or the liver, the organs responsible for their elimination.

Erroneous results of TM measurements are more likely to cause undesirable effects than other laboratory tests. Their misinterpretation may lead to unnecessary clinical investigations and, above all, may cause considerable psychological stress for the patient due to the supposition of a probable diagnosis of cancer or progression of the disease. To aid in the proper interpretation of TM results and to differentiate between malignant and non-malignant origins, the Barcelona criteria of 1994 proposed three general rules [1]:

1) The establishment of high-risk cut-off levels above which there is a significant probability of cancer.
2) The identification of the causes of false positives, with a special focus on the general and specific conditions that can affect the concentration of each marker.
3) The monitoring of changes in the concentration of the marker. In case of malignant origin the concentration tends to increase over time, but in the case of a false positive result it remains stable or decreases. Therefore, monitoring the marker over time can help to distinguish between true and false positives and can make a significant contribution to clinical decision-making

The increase in concentration does not occur in all markers in the same way, even in identical conditions. For example, patients with kidney failure can show TM values that only narrowly exceed the URL, but this condition may have a notable effect on certain TMs which may present values similar to those observed in metastatic patients. Gaining insight into the factors that influence each marker, as well as the extent of their impact, is essential. To enhance diagnostic accuracy, it is vital to implement criteria that are specific to the marker in question and take into account the patient's clinical status, and to apply distinct threshold values when available.

In addition, false positives can be produced by preanalytical conditions such as inappropriate timing, specimen type, handling, and data-entry errors. It is at this preanalytical stage that errors are most frequent [2]. In the analytical phase, false positive results can be produced by methodological issues associated with the reliability of the measurement system, the lack of antibody specificity, and analytical interferences (cross-reactions) with similar molecules. The use of different methods for TM measurement poses another significant challenge. Ideally, results obtained with different methods would be fully interchangeable, but between-method variability for certain TMs may exceed 20%. This point is crucial during the follow-up of cancer patients.

2. Material and methods

The current study is an update of the review carried out in 2011 [3], expanded to include novel biomarkers and recent data regarding pathophysiological and methodological factors that can affect the concentrations of the circulating TMs most frequently used in clinical practice. The review is a continuation and refinement of the previous work [3]: tumor markers and pathological conditions are reviewed and expanded with a protein induced by vitamin K absence-II (PIVKA-II), with human epi-

didymis protein 4 (HE4), as well as changes in tumor markers in disease states, including SARS-CoV 2 and diabetes. With this purpose in mind, we carried out a Pubmed search for relevant articles and collected information published between Januray 1970 and February 2023 with the following key words: Tumor Markers, α-fetoprotein (AFP), β2-microglobulin (β2-M), cancer antigen 125 (CA 125), cancer antigen 15-3 (CA 15-3), cancer antigen CA 19-9 (CA 19-9), cancer antigen CA 72-4 (CA 72-4), carcinoembryonic antigen (CEA), chromogranin A (CgA), Chorionic gonadotropin (hCG), cytokeratin 19 fragment (CYFRA 21-1), neuron-specific enolase (NSE), HE4, serum HER2 (sHER2), squamous cell carcinoma antigen (SCCA), PIVKA-II, pro-gastrin-releasing peptide (ProGRP), prostate-specific antigen (PSA), protein S-100 (S-100) and thyroglobulin (Tg), false positive, pulmonary benign disease, gastric benign disease, gynecological benign disease, pancreatitis, gastritis, hepatitis, benign liver disease, ascites, chronic renal failure, acute renal failure, kidney disease, benign lung disease, pneumonia tuberculosis, pleural effusion, evaluation, diabetes, hypoglycemia, increase concentrations, anemia, pregnancy, skin benign disease, brain damage, COVID 19, SARS-CoV-2, vitamin deficiency. Up to 88 new references were added.

The clinical conditions most likely to increase circulating TM concentrations in the absence of cancer are described in Table 1.

3. General recommendations/general causes of false positives

The liver and kidneys are vital organs involved in the efficient removal of TMs from the body. By measuring certain biological values related to these organs, such as the concentration of aspartate-aminotransferase and alanine-aminotransferase, creatinine or the glomerular filtration rate, it is possible to identify their functional alterations and assess the impact these alterations have on clearance.

In addition, the pancreatic function can be effectively evaluated by measuring the concentrations of α-amylase and triacylglycerol-lipase. These values can aid in identifying elevated TM concentrations associated with pancreatic disease. It is also necessary to determine the standard maximum concentrations of TMs for comparison with the values observed. Not all these situations cause the same increases; for example, in the absence of cancer, the CA 19-9 antigen concentration may present values 1,000 times above the URL in cholecystitis [4], although in most cases the increase is smaller: it may be five times above the limit [5], and or in exceptional cases ten times above it [6].

Additionally, erroneous results may occur due to endogenous interferences. If the clinical suspicion does not match the abnormal TM value, the possibility of an analytical error should be considered; communication between clinical and laboratory staff is absolutely essential. Interferences may occur due to the presence of cross-reacting substances or antianalyte or antireagent antibodies [7].

The mechanism of interference and the severity of its impact depend both on assay design and on the nature of the interfering antibody. Some patient serum samples contain human anti-mouse antibodies (HAMA), heterophile antibodies or antibodies associated with rheumatoid disease.

4. α-Fetoprotein (AFP)

AFP is a glycoprotein synthesized by the yolk sac and by hepatocytes during fetal development. At birth, AFP levels are elevated, with concentrations reaching 48,400 ng/mL in full-term infants and up to 158,510 ng/mL in premature infants. Later these levels decline and stabilize, reaching adult physiological levels between 8 and 24 months of age [8, 9].

At the onset of pregnancy, AFP levels are low, and maximum levels (200-300 ng/mL) occur between 30-32 weeks of gestation, reaching up to 30 times the normal value in adults. The reference value in pregnant women is influenced by several physiological variables, including ethnicity and the number

Table 1
Main causes of elevated tumor marker levels in the absence of neoplasia

	AFP	β-hCG	β_2M	CA 15-3	CA 19-9	CA 125	CA 72-4	CEA	CgA	CYFRA	HE4	HER-2	NSE	PIVKA II	Pro-GRP	PSA	S-100	SCC	Tg
Pre-analytical/iatrogenic	+[1]	+[2]	ND	ND	ND	+[3]	++++[4]	ND	+[5]	++[5]	ND	ND	ND	++[6]	ND	+[7]	ND	ND	ND
Liver disease	++++	+	++	++	++++	+	+	+	+	++	+	+	+	+	+	ND	++	+	ND
Renal failure	ND	++++	++++	+	++	++	++	++	++	++	++++	++	++	++++	++	++/-**	++++	+++	ND
Pneumonitis/Pulmonary fibrosis	ND	ND	ND	++++	++	++	+	++	+	++	+	ND	+	ND	+	ND	ND	ND	ND
Cystic fibrosis	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	ND	ND	ND	ND	ND
Effusions	ND	ND	ND	ND	+	++++	ND	ND	ND	+	+	ND	ND	ND	ND	ND	ND	++	ND
Pneumonia/COPD/Tuberculosis	+	ND	+	ND	++	++	ND	+	+	+	+	ND	+	ND	+	ND	ND	+	ND
Pancreatitis	ND	ND	ND	+	+++	ND	+	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Gastrointestinal diseases	ND	ND	ND	+	+++	+	+	+	++	ND	ND	ND	ND	ND	+	ND	ND	ND	ND
Hypothyroidism	ND	ND	ND	ND	ND	+	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hyperthyroidism	ND	ND	ND	+	ND	ND	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vitamin B_{12} deficiency	ND	+*	ND	++++	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vitamin K deficiency	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	++	ND	ND	ND	ND	ND
Endometriosis/gynaecological diseases	ND	ND	ND	+	++++	++++	++	+	+	ND	+	ND	ND	ND	ND	ND	ND	+	ND
Pregnancy	++++	++++	ND	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	++
Autoimmune diseases	+	++	++	+	+	++	ND	+	+	ND	++	ND	+	ND	ND	ND	+	+	++++
Haemolysis	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+++	ND	ND	ND	ND	ND	ND
Prostatitis/HBP	ND	ND	ND	ND	ND	ND	ND	ND	++	ND	ND	ND	ND	ND	ND	+++/+	ND	ND	ND
HIV/CMV/Viral infection	ND	ND	+++	ND	ND	ND	ND	ND	+	ND	+++	ND	ND	ND	ND	ND	ND	ND	ND
cardiovascular diseases	ND	ND	ND	ND	ND	++++	ND	ND	++++	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
cardiorespiratory arrest	ND	ND	ND	ND	ND	ND	ND	+	ND	ND	ND	ND	++++	ND	ND	++++	++++	ND	ND
Skin disease	ND	ND	+	+	ND	+	ND	ND	ND	ND	+	ND	ND	ND	ND	ND	++	++++	ND
Brain injuries	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	ND	ND	ND	+++	ND	ND
COVID 19	ND	ND	++	++	++	++	+	++	ND	++	++	ND	+	ND	ND	ND	ND	ND	ND
Diabetes	ND	ND	ND	+	+	+	+	+	ND	++	ND	ND	ND	ND	ND	ND	ND	ND	ND
Pre-eclampsia	+++	ND	ND	ND	ND	ND	ND	ND	ND	++	ND	ND	ND	ND	ND	ND	ND	ND	ND

AFP=α-Fetoprotein; β-hCG=Chorionic gonadotrophin (β-chain); β2M=β2-Microglobulin; CA 15-3 = Carbohydrate antigen15-3; CA 19-9 = Carbohydrate antigen 19-9; CA 125 = Carbohydrate antigen 125; CA 72-4 = Carbohydrate antigen 72-4; CEA = Carcinoembryonic antigen; CgA = Chromogranin A; CYFRA = antigen CYFRA 21-1; HE4 Human epididymis protein 4; HER-2 = HER-2/neu oncogenic protein; NSE = Neuron specific enolase; PIVKA II = Protein induced by vitamin K absence-II; Pro-GRP=Progastrin releasing peptide; PSA = Prostate specific antigen; S-100 = protein S-100; SCCA = Squamous cell carcinoma antigen; Tg = Thyroglobulin; ND = Not described; +=increase of tumor marker up to 2 times the upper reference limit (URL); ++=increase of the tumor marker between 2 and 5 times the URL; +++=elevation of the tumor marker between 5 and 10 times URL; increase of tumor markers more than 10 times the URL; *Only described for the -hCG free fraction; Reduction of PSAL/PSAT ratio in dialysis patients with low-flux membranes; [1]Hepatotoxic drugs and chemotherapy; [2]Abdominal surgery; [3]Marijuana consumption; [4]Treatment with Corticosteroid, ibuprofen and colchicine in patients with pericardial effusions and colchicine in patients with familial Mediterranean fever; [5]Treatment with omeprazole; [6]Treatment with warfarin; [7]Prostatic massage, transurethral resection; COPD = Chronic obstructive pulmonary disease; BPH = Benign prostatic hypertrophy.

of fetuses. African women tend to have high concentrations, while Asians have lower concentrations than Caucasians. The concentration of AFP is approximately twice as high in multiple than in single pregnancies. Additionally, significantly higher AFP concentrations are observed in pregnancies complicated with eclampsia [8–10].

AFP is a widely used marker for the screening of fetal congenital anomalies. Elevated levels may indicate neural tube defects, omphalocele, gastroschisis, or fetal intestinal obstruction. Conversely, low levels are associated with an increased risk of Down syndrome [11]. In adults, AFP concentrations may be increased in benign liver diseases and inflammatory processes causing liver damage. Examples are cell necrosis and regeneration caused by viral hepatitis (A, B, C, cytomegalovirus), acute ischemic liver failure, autoimmune disease, drug-induced hepatotoxicity, chronic hepatitis of any cause, cirrhosis, or liver abscesses [3, 12]. Although these increases are typically moderate (<100 ng/mL) [13], higher levels have also been observed in various benign conditions. Yoon et al. reported a case of a patient with chronic acute hepatitis B with an AFP value of 2,350 ng/mL in whom the absence of tumor was confirmed [14]. In children and adolescents, elevated concentrations of AFP have been reported in hereditary tyrosinemia type I (values 140 times the URL) [15], in hereditary persistence of AFP (with values 10 times above the URL and reaching 1,000 ng/mL), in ataxia telangiectasia (with values between 20 or 30 times the URL and occasionally reaching 1,000 ng/mL, and rising slightly with age), in ataxia with oculomotor apraxia type II (with values not exceeding 60 ng/mL and not rising with age, in contrast to ataxia telangiectasia) and also modest increases in some cases of ataxia with oculomotor apraxia type I where marker values are usually within the normal range. Additionally, concentrations of AFP above the reference range have been described in some mitochondrial ataxias, specifically those with mutations in the POLG and C10orf2 nuclear genes [15].

Significant increases in AFP levels in cholestatic disorders such as extrahepatic biliary atresia and idiopathic neonatal hepatitis have been observed in infants aged 1–4 months [9, 16] and also in infants aged 1-6 months undergoing extensive intestinal resection [9]. In the latter case, it appears reasonable to assume that, given the liver and the intestine derive from the same embryonic layer, a transient increase in AFP may occur in the process of intestinal cell regeneration [9]. In the aforementioned article, Wojtulewicz et al. reported the case of a child undergoing partial ileal resection due to necrotizing enterocolitis who reached a minimum AFP value of 1,079,367 ng/mL 37 days post-surgery, and a maximum of 1,646,028 ng/mL 49 days post-surgery. AFP increases have also been reported in a patient with gynecomastia and nodular focal hyperplasia (with values up to six times above the URL) [17]; in hepatic mesenchymal hamartomas [18]; and in systemic lupus erythematosus, Hirschsprung's disease and Beckwith-Wiedemann syndrome [19]. Substantial increases were reported in a patient with peritoneal tuberculosis [20]. Increases in AFP have also been reported in patients with Fanconi's anemia [18].

The intake of hepatotoxic substances such as arsenic or aflatoxin B1 (which may be found at doses higher than the permissible level in the composition of some dietary supplements) can lead to an increase in AFP levels [21].

AFP levels are not affected by kidney failure, even in patients with advanced stages or in renal replacement therapies such as hemodialysis, peritoneal dialysis, or kidney transplant [22].

Research on patients with COVID-19 has shown that the virus has no impact on AFP concentration [23].

5. Chorionic gonadotropin (hCG)

hCG is a member of the glycoprotein hormone family which includes thyrotropin (TSH), follitropin (FSH) and lutropin (LH). These hormones are characterized by a shared α subunit, while their biolog-

ical activity is determined by the unique β subunit [24]. Several isoforms of hCG are differentiated according to the origin of their synthesis, biological function, mode of action through receptors, number of subunits and glucose composition. Despite these differences, all hCG isoforms share a common sequence of amino acids in both subunits. These isoforms are the "intact" hCG (hCGi), sulphated hCG, intact hyperglycosylated hCG (hCG-H), β-free choriogonadotropin (fβ-hCG) and β-free hyperglycosylated choriogonadotropin (fβ-hCG-H). During metabolism, these isoforms give rise to different fragments or molecular forms, such as the C-terminal peptide or the β core fragment, which are eliminated mainly in the urine [25, 26].

The results can vary considerably depending on the type of immunoassay used, as different assays detect different types of molecules. To accurately detect the presence of tumors, the use of an immunoassay that can detect as many isoforms and fragments as possible is recommended so to minimize the risk of false negative results.

When neoplasia has been ruled out and a positive hCG result is obtained in the absence of pregnancy, the result must be confirmed using an alternative analytical method, measuring the hormone in urine or ruling out the presence of heterophilic antibodies in serum. Heterophilic antibodies can react with immunoglobulins in immunoassays and give erroneously elevated results. To counteract this, most manufacturers incorporate murine-origin IgG immunoglobulins in immunoassays in order to block heterophile antibodies, but sometimes their concentrations are so high that they can also cause interference [27].

High levels of β-hCG have been found in patients with chronic kidney failure and those undergoing hemodialysis, with levels ranging from three to ten times the reference value. This is probably due to a decrease in the hCG clearance caused by reduced kidney filtration and elimination [28–30].

In perimenopausal and postmenopausal women, slightly elevated hCG values are frequent due to hypophysial production in this population. The prevalence of hCG levels of 5 IU/L or higher in women between the ages of 41 and 55 is estimated to be between 0.2% and 0.3%, while in older patients the percentage with values above 5 IU/L ranges between 8% and 10% [31].

Other conditions can also cause falsely increased levels of this marker, including marijuana use [32], consumption of weight loss dietary supplements or performance-enhancing drugs [33], systemic lupus erythematosus [34] and the administration of blood transfusions from pregnant donors with high levels of β-hCG [35].

The hCG family syndrome is a rare hereditary disease that affects both men and women, with an estimated prevalence of 1 in 60,000. Affected patients produce a mutant form of hCG with multiple alterations in the CTP region, which results in persistently elevated levels of hCG, ranging from 10 to 200 UI/L [36].

Knight et al. reported high levels of β-hCG in patients with IgA deficiency, up to 15 times higher than the URL. The increases are also related to the presence of heterophile antibodies in these patients [37]. Persistently high levels of hCG were reported in three patients diagnosed with Munchausen syndrome, but the results of serial hCG tests (in both serum and urine) were inconsistent: the levels fluctuated, rising and falling rapidly, which suggested an exogenous administration of recombinant hCG [38, 39].

6. β2-microglobulin (β2-M)

β2-M is a low molecular weight protein (11.8 KDa), non-covalently bound to the light chain of the major histocompatibility complex type I. It is present in all nucleated cells in the body, although its concentrations may be higher in certain cells [40]. The primary elimination route for β2-M is the kidney; thus, impairment of kidney function leads to a significant increase in β2-M concentration. Patients with kidney failure undergoing hemodialysis may present values 20 times above the URL, occasionally

even 30 times higher [22, 41]. Increased levels have also been reported in workers exposed to cadmium, which was related to the degree of kidney failure [42]. In certain conditions that activate lymphocytes, such as viral infections, β2-M levels may also rise. Increases in β2-M levels have also been described in infections caused by the human immunodeficiency virus (HIV) [43], and by cytomegalovirus [44, 45]. Studies have reported that the concentration of β2-M can change in parallel with the treatment of hepatitis B virus infections [46, 47]. Collazos et al. [48] proposed the use of β2-M concentrations to evaluate the treatment of tuberculosis, a disease that also causes this marker to increase.

Scangolari et al. [49] reported that the concentration of β2-M was twice its normal value in patients with hepatitis C or multiple sclerosis who were treated with interferon-γ.

In autoimmune diseases such as systemic lupus erythematosus, Żychowska et al. [50] observed an increase of up to 8 mg/L in patients presenting with arthritis or vasculitis, with mean concentrations that were twice as high as in patients without these complications. Increases have also been reported in other autoimmune diseases such as inflammatory bowel disease (in both ulcerative colitis and Crohn's disease) with concentrations more than 50% higher in patients with active disease than in those with controlled disease [51]. During the COVID-19 pandemic, increases of up to two to four times the URL were found in patients infected with SARS-CoV-2 [52].

7. Cancer antigen CA 15-3 (CA 15-3)

CA 15-3 is a high molecular weight (300-450 KDa) protein, which is a component of the transmembrane receptor MUC-1 and has cell adhesion functions [53]. In patients with cobalamin (vitamin B12) deficiency and macrocytosis, CA 15-3 concentrations may be up to ten times higher than the URL. In these patients, higher lactate dehydrogenase concentrations have been observed [6]. Other hematological diseases associated with ineffective erythropoiesis, such as β-thalassemia and sickle cell anemia, have also been associated with CA 15-3 concentrations which are more than six times higher than the URL [54].

Granulocyte colony-stimulating factor (G-CSF) treatment can result in a temporary increase in the concentration of CA 15-3 to twice the URL, with a return to normal values after discontinuing treatment [55]. In patients with some inflammatory myopathies, up to 22% presented CA 15-3 antigen values above the URL [56]. Collazos et al. [57] observed elevated CA 15-3 concentration in 11% of patients with cirrhosis and in 6% of patients with liver disease without cirrhosis. In another study, these same authors [58] found that patients with immunoglobulin A concentrations above the URL exhibited higher CA 15-3 concentrations. Elevations of up to ten times the URL in interstitial lung disease have been reported, and twice this limit in collagen dislocation-associated pneumonitis [59]. Kruit et al. [60] reported a good correlation between high levels of CA15-3 and Krebs von den Lungen 6 (KL6), a mucin-like glycoprotein that has been proposed as a marker of pulmonary epithelial cell injury. In systemic sclerosis, 14% of false positive results were attributed to high concentrations of C-reactive protein and antinuclear antibodies [61]. In polymyositis, concentrations up to five times the URL have been reported [57].

Increases in CA 15-3 concentration have also been described during the menstrual cycle and benign gynecological diseases such as ovarian cysts. The proportions of women with a concentration of CA 15-3 above this limit were 3%, 7%, 6% and 6% in the menstrual, follicular, periovulatory and luteal phases respectively [62]. Even though there were no significant differences between the phases, evaluation of CA 15-3 is recommended during the menstrual phase, in order to reduce the number of false positives. In kidney failure there are discrepancies between the references consulted: while some authors report that 4.5% of patients exceeded the URL by up to five times [62], others found no differences compared to healthy individuals [5]. Molina et al. [63] reported an increase in values of up to twice the URL in

benign gastrointestinal diseases, including ulcerative colitis, Crohn's disease, pancreatitis, hepatitis, cirrhosis, and cholecystitis.

During the COVID-19 pandemic, increases of up to two to four times the URL were found in patients infected with SARS-CoV-2. Values above 80 U/mL were a factor of poor prognosis, being associated with pulmonary fibrosis [64].

8. Cancer antigen CA 19-9 (CA 19-9)

CA 19-9 was first isolated from the colon carcinoma cell line SW1116 by Koprowski et al. in 1979 [65]. It is recognized by the monoclonal antibody 116 NS 19-9. The structure of CA 19-9 was later identified by Magnani et al. [66] as a sialylated lacto-N fucopentaose II, an oligosaccharide related to the Lewis A blood-group substances. Individuals who have a Lewis a-b phenotype do not express this antigen. CA 19-9 is undetectable in 91.7% of Lewis-negative patients [67] suggesting that CA 19-9 may not be a reliable marker for the diagnosis and follow-up of this particular subgroup of patients.

CA 19-9 is a widely used tumor marker for gastrointestinal, biliary and ovarian cancers, particularly those with mucinous histology [68, 69]. However, values of CA 19-9 above the URL of 37 U/L have also been reported in patients with benign conditions as well as in some healthy individuals. Del Villano et al. [70], for instance, found CA 19-9 concentrations above the URL in six out of 1,020 healthy subjects. In particular, the specificity of CA 19-9 for cancer diagnosis may be limited in patients with certain benign conditions such as pancreatitis, cholangitis, or liver cirrhosis. The main causes of CA 19-9 false positives are hepatobiliary diseases and pancreatitis (both acute and chronic), particularly when the patient has obstructive jaundice. Indeed, the use of this tumor marker is unreliable in patients with alterations of the bile duct [71, 72]. Klapdor et al. [73] observed increased CA 19-9 levels in 88% of patients with acute pancreatitis and in 5% of chronic pancreatitis, while Heptner et al. [74] reported increases in 27% of patients with acute pancreatitis, in 10% of those with chronic pancreatitis, and in 50% of exacerbations in patients with chronic pancreatitis. However, Teng et al. [75] reported that the incidence of pancreatic cancer in patients with acute pancreatitis rises proportionally to CA 19-9 levels. Barone et al. [76] found that 54% of patients with extrahepatic benign obstructive jaundice had CA 19-9 levels >37 U/mL with 34% having levels >75 U/mL and >10% having levels >400 U/mL. Although there was no correlation between bilirubin levels and CA 19-9, some studies propose the use of C-reactive protein to adjust CA 19-9 levels for better diagnostic accuracy in obstructive jaundice [77]. Extremely high CA 19-9 concentrations have been reported in some non-cancerous conditions. Murohisha et al. [4] described a patient with a gallbladder stone complicated by cholangitis with a CA 19-9 level of 40,000 U/mL, while Moshref et al. [78] reported a concentration of 21,068 U/mL in a patient with Mirizzi syndrome, an unusual complication of gallstone disease. In addition, Akdogan et al. [79] found a concentration of 35,000 U/mL in a patient with cholangitis and a pancreatic pseudocyst. A recent study analyzed the causes of elevated CA 19-9 in patients without tumors or pancreatobiliary disease [80]. The study included 192 patients with a CA 19-9 >80 U/mL and estimated that the most common cause of the increase was liver disease, followed by gynecological, pulmonary, endocrine, and spleen diseases. The increase in the marker was unexplained in 45 patients; in 35 cases the CA 19-9 subsequently normalized, but 10 cases the increase persisted.

These findings corroborate those of previous reports, such as those of Petit et al. [81] who observed CA 19-9 increases in patients with decompensated diabetes mellitus, while Takayama et al. [82] recorded increased levels in patients with benign lung diseases, specifically idiopathic pulmonary fibrosis (81%), bronchiectasis (59%) and tuberculosis (52%). CA 19-9 false positives can also occur in patients with cysts and pseudocysts in various locations [83, 84], due to the high concentration of this substance inside these lesions. CA 19-9 elevations have also been observed in patients with kidney

failure [5], endometriosis [85], and rheumatological [86] and benign gastrointestinal diseases [87], and have been associated with excessive tea consumption [82]. More recently, increased CA 19-9 levels were observed in patients with COVID-19 [23].

9. Cancer antigen CA 72-4 (CA 72-4)

CA 72-4 is a high molar weight mucin, detected using monoclonal antibodies B72.3 and CC-49. According to Filella et al. [89, 90] 5% of pregnant women present CA 72-4 concentrations of more than twice the URL.

Those authors also reported values above this limit in patients with various non-malignant conditions, including 5% of patients with benign gastrointestinal or heart disease, 4% with hepatopathies, 6% with pulmonary disease (especially pneumonia, 9%), and 10% in benign gynecological diseases (especially ovarian cyst, 25%) and found that the majority of patients with elevated CA 72-4 suffered from rheumatoid disease [90]. Arthritis is a frequent source of increased CA 72-4 levels. Halm et al. [91] reported that between 3% and 7% of patients with pancreatitis presented values above the URL. Yang et al. [92] reported slightly increased concentrations in 4% of patients with gastric and duodenal ulcers and gastritis. Balaban et al. [93] found that 50% of patients with familial Mediterranean fever had CA 72-4 antigen concentrations exceeding the URL. Several pharmacological treatments have been associated with increased CA 72-4 concentrations. In patients with pericardial effusion treated with ibuprofen, a notable increase in CA 72-4 concentrations was observed, exceeding the URL by more than ten times, which then fell after the discontinuation of the treatment [94]. Treatment with corticosteroids and proton pump inhibitors has also been identified as a potential cause of elevated CA 72-4 concentrations [95]. A recent study reported that gout patients receiving colchicine had significantly higher serum CA 72-4 levels than healthy controls or gout patients who received another treatment or none at all [96].

10. Cancer antigen CA 125 (CA 125)

CA 125 is a high molecular mass glycoprotein present in structures derived from Müllerian ducts and the mesothelium [97, 98]. It is primarily used for the management of ovarian cancer, generally in combination with other diagnostic tests and imaging techniques [99]. The diagnostic accuracy of CA 125 concentration is often hindered by false-positive results, caused mainly by serous effusions and fluid retention. In a study by our group [100] patients with benign effusions showed substantial increases in CA 125, surpassing the URL by an average of five to six times and occasionally by up to 100 times. Comparable values have been described in patients with liver diseases and ascites [101], while only a minority (10%) of patients with liver diseases without ascites presented values above the URL and none exceeded concentrations ten times above this value. Notable increases have also been reported in severe hypothyroidism, particularly when accompanied by effusion [102]. In benign ovarian disease, the concentration of CA 125 may surpass the URL by two or three times [103], while in Meigs syndrome values up to 50 times the URL have been reported [104]. Notable elevations in CA 125 concentration have been observed in patients with congestive heart failure, presenting positive correlations with disease severity and also with brain natriuretic peptide (BNP) concentration. False positives were not observed in patients defined as class I or II in the New York Heart Association classification (NYHA); in NYHA class III patients, mean values were close to twice the URL, while class IV patients had values seven times above this limit [105]. In this setting, Nuñez et al. [106] found that 66% of patients had values above the cut-off limit, and at six months, the hazard ratios (HRs) for death were 3.25, 4.91 and 8.41 for the 2nd, 3rd and 4th quartiles, respectively.

Increases in the concentration of this marker have been linked to inflammation caused by water retention, a situation that allows for the identification of patients' response to diuretic treatment [107].

Although increases in this marker were reported during the menstrual cycle in 5% of women, their values were less than twice the URL [62]; during this phase the reported rate of false positives was 5.5%, while in the follicular and lutein phases it was 2%. However, the authors did not report an increase in CA 125 concentration above the URL during the peri-ovulatory period. The lowest number of false positives was found in the follicular, periovulatory, and lutein phases, in contrast to the behavior observed with CA 15-3 antigen. As a result, it is difficult to recommend a particular stage of the menstrual cycle for the measurement of CA125 and CA15-3. Talbot et al. [108] reported CA125 increases up to three times the URL in 62% of patients three weeks after abdominal surgery.

Filella et al. [5] reported that CA 125 concentration rose in 17% of patients with kidney failure who were not undergoing hemodialysis and in less than 10% of patients who were receiving this treatment. The authors observed moderate elevations in CA 125 concentration, with the levels up to two and up to five times above the URL in patients with and without hemodialysis, respectively. Increases in the concentration of this marker have also been reported in lung diseases, including active tuberculosis, with values up to four times the URL.

Mean CA 125 concentrations of more than twice the URL have been described in chronic obstructive pulmonary disease, pneumonia, interstitial lung disease, and lupus erythematosus [109, 111]. During pregnancy, the concentration of this TM increases after the tenth week of gestation and remains high. Klug et al. [111] described false positives caused by human anti-idiotypic immunoglobulin. During the COVID-19 pandemic, increases of up to three times the URL were reported in patients infected with SARS-CoV-2 [23].

11. Carcinoembryonic antigen (CEA)

CEA is a high molecular weight glycoprotein that belongs to the immunoglobulin family. It is expressed in various tissues, including the stomach, large intestine, pancreas, and lungs. Inflammatory processes or necrosis of these organs can release significant amounts of CEA and its concentration may raise above the URL. High concentrations of this TM have been reported in pancreatitis [112], diverticulitis [113], and peptic ulcer [114], where the levels may rise to up to four or five times the URL. Inflammatory bowel disease has been associated with an increased number of false positives, reaching values four to eight times the URL in severe cases [115].

Patients with cholecystitis showed increases in CEA up to 66 ng/mL (median 3.4 ng/mL, interquartile range 5.75 ng/mL), while those with chronic pancreatitis peaked at 14.0 ng/mL (median 2.27 ng/mL, IQR 1.97 ng/mL) [116].

Pneumonia caused by different microorganisms including bacteria [117], fungi [118, 119] and tuberculosis [120], has been linked to increases in CEA concentration to up to two or three times the URL. Elevated values have also been observed in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis [109]. In a study of 171 patients with COVID-19, 18% had values above the URL; fatal outcomes were associated with a mean CEA of 20 ng/mL (p25 = 14.7; p75 = 23), while survivors had a mean value of 10.9 ng/mL (p25 = 7.5; p75 = 16.1) [121].

The concentration of CEA rises in diseases that affect organs involved in its metabolism such as the liver, and in its elimination, such as the kidneys. Filella et al. [5] reported increases in CEA concentrations in patients with renal impairment, with a correlation between creatinine and CEA concentrations. More false positives were observed in patients treated with hemodialysis than in those that did not receive this treatment (47% vs. 30%), and treated patients had higher CEA concentrations (five times the URL, compared with three times in their untreated peers). Another organ involved in

the metabolism of CEA is the liver. George et al. [122] described CEA concentrations up to four times the URL in patients with fulminant hepatitis, with mean values 1.5 times this figure.

In obstructive jaundice, the mean values were found to be twice the URL [123]: patients with benign tumors, necrotizing cholangitis, and choledochal cysts had values above 20 mg/L, with the highest values recorded in patients with choledochal cysts. Collazos et al. [124] found increases in the concentration of this TM in 38% of patients with cirrhosis, with increases in 42% of patients at Child-Pugh stages B and C and in only 28% of those at stage A.

An increase in CEA concentrations was reported in 7% of patients with adnexal masses [125]. Amino et al. [126] described high concentrations of this TM in patients with hypothyroidism which correlated directly with the duration of the condition and inversely with thyroxine concentration. Patients with poorly controlled diabetes (HbA1 C>8%) had a higher proportion of false positives than their peers with well-controlled diabetes. However, the values in the poorly controlled patients returned to normal levels when glycemic control was restored [127].

Finally, certain false positives have been observed, sometimes with particularly high values, that cannot be attributed to any cause. For example, Shapiro et al. [128] reported a case with a CEA concentration of 44.9 mg/L, but the authors could not identify a reason. Trapé et al. [129] also reported a patient with diverticulitis and renal failure who had a CEA concentration of 42.0 ng/mL.

12. Chromogranin A (CgA)

CgA is secreted by the adrenal cells, hypophysis, pancreas, stomach, intestine, lungs, heart and prostate [130]. As a result, the main increases in CgA concentration in the absence of cancer are observed in diseases related to these organs such as hypertension, heart and liver failure.

In patients with benign prostatic hyperplasia, concentrations of CgA above the URL have been described [131, 132]. Patients with chronic hepatitis and cirrhosis of the liver may have CgA concentrations ten times above the URL [133]. Similarly, increased concentrations of this TM are also observed in patients with acute coronary syndrome [134, 135]. Additionally, CgA concentrations above the URL have been reported in patients with diseases affecting the respiratory tract, with concentrations above the URL in patients with chronic obstructive pulmonary disease [136], and in smokers with airway obstruction [137].

Patients with chronic renal failure may also show CgA concentrations above physiological values, particularly those undergoing hemodialysis [138, 139]. Spadaro et al. [140] found increases in CgA concentration in 92% of patients with chronic renal failure in patients, with values up to 30 times the URL.

CgA concentrations above the URL have also been found in patients with endometriosis and leiomyoma [141] and in patients with hyperthyroidism [142]. However, the use of antithyroid drugs can significantly lower these concentrations. Patients with autoimmune atrophic gastritis and inflammatory bowel disease, specifically in ulcerative colitis and Crohn's disease, also have increased CgA concentrations [143, 144]. Some publications [145, 146] report that the administration of low doses of omeprazole over a short period can raise the CgA concentration in men with endocrine or metabolic dysfunction, and medium- and long-term omeprazole therapy can increase CgA concentrations up to twice the URL [147].

Recently, De Lorenzo et al. [148] demonstrated that CgA increases in COVID-19 patients, and that the levels are related to the severity of the disease. It is important to note that CgA concentration can be affected by various pathological and physiological conditions, and its specificity may be strongly affected by several benign processes [149]. Therefore, the variability of CgA measurement in different conditions must be borne in mind.

13. Cytokeratin 19 fragment (CYFRA 21-1)

CYFRA 21-1 comprises the soluble cytokeratin 19 fragment which can be detected using BM 12.21 and KS19.1 antibodies. It has a molecular weight of 30KD and is expressed predominantly in the lung, as well as in mesothelial cells, and in many tumors of epithelial and mesenchymal origin [150]. The highest increases in the absence of neoplasia have been observed in various lung diseases. In interstitial pulmonary fibrosis, increases above the URL occur in 50% of cases, reaching values of 11.0 mg/L. In pulmonary fibrosis associated with collagen disease, 30% of patients had values above the URL, with increases of up to 20.0 mg/L [151]. Elevated levels of CYFRA 21-1 have also been reported in patients with tuberculosis, chronic obstructive pulmonary disease, emphysema, and in patients with radiation-induced pneumonitis [152].

In autoimmune alveolar proteinosis, CYFRA 21-1 levels can rise to 26 ng/mL, with an average increase of 11 ng/mL, which can be reduced by inhalation of granulocyte-macrophage colony stimulating factor (GM-CSF) [153].

False positives for CYFRA 21-1 may occur in patients with kidney failure [154], particularly in those receiving peritoneal dialysis; values above the URL were recorded in 73% of these patients, and in 57% of patients with hemodialysis [155]. Elevated levels of CYFRA 21-1 have also been observed in patients with diabetic nephropathy [156], benign pleural and pericardial effusions [157], cirrhosis of the liver and preeclampsia, where levels were related to the severity of the disease [158]. In the case of SARS-CoV-2 infection, Wei et al. [159] observed values above the URL. Specifically, severe cases exhibited an average increase of 3.3 ng/mL, whereas critical cases displayed an average increase of 3.9 ng/mL. Notably, the maximum value observed was 10 ng/mL, which was not surpassed in any of the cases studied.

14. Human epididymis protein 4 (HE4)

HE4, also known as WFDC2, is a member of the whey acidic protein four-disulfide core family (WFDC), and is believed to exhibit trypsin inhibitor properties. It is encoded by a gene located on chromosome 20q12–13 [160]. In its mature glycosylated form, the protein has a molecular weight of approximately 25 kD and is comprised of a single polypeptide chain with two WFDC domains.

It is expressed in various tissues, including the respiratory tract, kidney and ovary. This protein plays a critical role in innate immune defense and tumorigenesis [161]. Normal values are twice as high in postmenopausal women (140 pmol/L) than in premenopausal women (70 pmol/L) [161]. Kidney failure is the most important source of false positives; up to 85% of patients with kidney failure or a creatinine value above 1.3 mg/dL can present values more than 10 times higher than the reference range, the median concentration observed being 950 pmol/L [160].

Approximately 46% of heart failure patients presented slight increases in HE4, of the order of 300 pmol/L, and this protein was identified as a biomarker of myocardial fibrosis [162]. In patients with effusions, 35% may exhibit HE4 values that are three times above the cut-off point, with levels reaching up to 450 pmol/L [95, 160]. Among female smokers, 22% displayed false positive results approximately 20-30% above the URL. This finding highlights the importance of considering smoking when evaluating serum HE4 values [163]. Additionally, approximately 10% of patients with benign lung disease experience minor increases in HE4 levels, with values reaching up to 334 pmol/L [160]. Notably, recent studies have reported minor increases in HE4 in patients with COVID-19, with critical patients potentially exhibiting levels up to 300 pmol/L [164].

15. The oncogenic protein Her2/neu (HER2/neu)

The HER2/neu consists of an extracellular domain, a transmembrane domain and an intracellular domain with tyrosine kinase activity. This molecule is involved in mechanisms of tissue growth, survival and differentiation. It is overexpressed in 15-30% of breast carcinomas and in lung, colorectal, squamous cell, gastric, ovarian, bladder and pancreatic cancers [165, 166]. In patients with breast cancer, HER2 overexpression is linked to more aggressive behavior and poor prognosis [167]. The development of anti-HER2-targeted therapies has substantially enhanced the overall survival rate of patients with this subtype of breast cancer [168]. In this context, the HER-2 immunoassay in serum (sHER2), which quantifies the extracellular domain (ECD) of the protein, was granted FDA approval in 2000. Increased levels of this marker have been reported in benign pathology in 30-63% of patients with liver disease, including acute and chronic hepatitis, cirrhosis, cholelithiasis, and also in benign breast pathology, renal failure, gastric ulcer, and systemic lupus erythematosus [169, 170]. Furthermore, Wen et al. reported increased concentrations of this marker in patients with coronary artery disease, particularly in those with stenosis involving two or more vessels [171]. ErbB2 is also known to play an important role in lipid and glucose metabolism and is involved in the pathogenesis of insulin resistance, particularly in the context of obesity. Several studies have reported slightly elevated levels of HER2 in patients at risk of developing diabetes or in those recently diagnosed with type 2 diabetes mellitus [172, 173].

The HER2 transmembrane receptor is minimally expressed in normal epithelial cells, but during pregnancy, it is overexpressed in the fetal and placental epithelium. Tse et al. reported higher concentrations of HER2 in pregnant women with preeclampsia compared to controls, probably due to the greater increase in placental apoptosis associated with this condition [174]. Moreover, the presence of anti-animal antibodies/anti-mouse antibodies (HAMA) may also interfere with immunoassays that measure the soluble fraction of the HER2 receptor and may lead to false positive results [175].

16. Neuron-specific enolase (NSE)

NSE is a glycolytic enzyme that catalyses the conversion of 2-phospho-D-glycerate to pyruvate phosphoenol. There are five known enolase isoenzymes, which comprise the combination of three subunits: α, β and γ [176], The isoenzyme comprising two g subunits is mainly synthesized in central and peripheral neurons, as well as in neuroendocrine cells. The most common cause of false positives for NSE is sample hemolysis due to a high presence of the enzyme in erythrocytes [177]. Patients with kidney failure may also show elevated NSE concentrations, with false positive rates of up to 36% and values two to three times above the URL [5]. Muley et al. [178] reported that patients with benign lung disease had NSE concentrations three times above the URL. In addition, increased concentrations were found in 27% of tuberculosis patients [179].

The brain has a high NSE content, which is present in central and peripheral neurons. Thus, in traumatic lesions, hypoxia or hypoglycemia causing neuronal damage, its plasma concentrations are high.

Vos et al. [180] found mean NSE concentrations in patients with head trauma that were twice the URL; values of this marker above 21.5 mg/L were considered a sign of poor prognosis. In addition, NSE concentrations up to ten times the URL were observed in stroke patients [181]. Severe insulin-induced hypoglycemia can lead to NSE concentrations five times above the URL in some patients [182]. In patients resuscitated after cardiopulmonary arrest, NSE values increased until the third day; among the patients with severe neuronal damage the medians on the first, second, and third days were

higher in those with severe brain injury (22.6 vs 33.6, 18.1 vs 76.6 and 9 vs 80 ng/mL respectively). Values of up to 500 ng/mL on the third day have been described [183]. In liver disease, 5% of patients may present NSE values of twice the URL [184], and in systemic sclerosis, one-third of patients may have peak NSE values five times above the URL [185].

17. Protein induced by vitamin K absence-II (PIVKA-II)

PIVKA-II is a decarboxylated precursor protein of vitamin K-dependent coagulation factors that is induced by vitamin K deficiency [186]. The liver releases PIVKA-II into the bloodstream; however, due to its lack of calcium-binding capacity, it remains inactive.

Measuring PIVKA-II concentration is a useful way to detect the presence of subclinical vitamin K deficiency, and it can also identify deficiencies before they lead to coagulopathies [186]. PIVKA-II serum concentrations are increased in some neoplastic diseases such as in hepatocellular carcinoma (HCC) and pancreatic cancers. Elevated levels of PIVKA-II are associated with more advanced stages of HCC and a poorer prognosis. [187].

The false positives found in the case of PIVKA are mainly related to vitamin K deficiency. Research indicates that PIVKA-II levels are elevated in patients treated with warfarin, indicating that PIVKA-II may serve as a follow-up marker for such patients [188].

PIVKA-II concentrations can be significantly elevated in dialysis patients compared to healthy controls, with levels up to 37 times higher than normal [189]. Thus, kidney failure may artificially increase PIVKAII, making it a less reliable biomarker in this population. In addition, slight increases in PIVKA-II values have also been reported in other benign conditions, such as cystic fibrosis [190]. In a study involving 3015 Asian patients with PIVKA-II values >40 mAU/mL, 1054 did not have HCC. In these cases, the median levels of PIVKA-II and the interquartile range were 85 mAU/mL (53-207.5 mAU/mL) in cirrhosis, 61 mAU/mL (46-107 mAU/mL) in viral hepatitis, 62 mAU/mL (47-109.5 mAU/mL) in benign nodules and 53 mAU/mL (43-117 mAU/mL) in adipose infiltration. Combining AFP and PIVKA-II improves the diagnostic accuracy of HCC due to the high specificity of PIVKA-II [191].

However, it is a important to stress that PIVKA-II is a rarely used marker, and the references to false positives are limited; therefore, the results should be interpreted with caution.

18. Pro-gastrin-releasing peptide (Pro-GRP)

Pro-GRP is a 27 amino acid peptide that shares homology with bombesin, which was originally isolated from swine stomach. Pro-GRP appears to play an important role in metastatic dissemination, either through autocrine signaling or through cell-cell interaction. However, its main drawback as a biomarker is its instability in the bloodstream. On the other hand, the pro-peptide, Pro-GRP, is stable in the bloodstream and can be measured using immunoassay [192].

However, it is important to bear in mind that certain diagnostic instruments detect a labile epitope that remains stable for only two hours at room temperature in serum and more than six hours in plasma with EDTA [95].

Kidney failure is the most common source of false positives, with a clear relationship between creatinine levels and Pro-GRP concentrations which can reach values of 300 pg/mL [3, 193, 194]. The specificity of Pro-GRP is high in patients without malignancy, as long as kidney failure is ruled out. In liver and lung benign diseases, only a small percentage of patients present mild Pro-GRP elevation, with levels never exceeding 80 pg/mL [3, 193, 194].

19. Prostate-specific antigen (PSA)

PSA, also called human kallikrein 3, is part of the kallikrein family and is mainly produced by prostate epithelial cells, although it is also expressed by other tissues. PSA is the marker of choice in the management of patients with prostate cancer, although increased levels have sometimes been observed in patients with benign prostate disease. Acute prostatitis [195] is characterized by very high levels of PSA, which return to normal once the infection has resolved. However, PSA levels are also high in 25-50% of patients with benign prostatic hyperplasia, especially in cases of acute urinary retention or urinary tract infection [196, 197].

PSA may also be increased by manipulations of the prostate gland, including prostate massage, prostate biopsy, transurethral resection, and cystoscopy [198, 199]. In contrast, in most cases, there are no significant alterations in PSA concentrations following a digital rectal exam; however, it is advisable to wait a few days between the rectal exam and the measurement of the PSA to avoid any potential minor effects on PSA levels [2].

PSA false positives related to non-prostate pathology are uncommon. However, high levels have been reported in women with acute pancreatitis or pancreatic cancer [200]. Danışman et al. [201] reported that patients with end-stage renal disease or those undergoing hemodialysis do not have increased PSA levels. Nor did Bruun et al. [202] find any influence of hemodialysis on PSA levels, although they did report increases in free PSA levels. In contrast, other authors have observed that hemodialysis with low-flow membranes does not eliminate PSA and that its concentration rises after this procedure [203].

Although liver disease does not generally appear to be a common cause of false positives in this TM, elevated levels of PSA have also been reported in patients with acute type A hepatitis [204]. Inci et al. [205] reported decreased levels of PSA in patients with liver cirrhosis in relation to reduced prostate volume in these patients and also lower testosterone and protein levels. Patients with diabetes presented lower PSA levels than healthy subjects [206], while an inverse correlation was observed with body mass index, with lower PSA concentrations in obese patients [207]. Patients with heart disease or those undergoing cardiac surgery may present increased PSA levels [208]. Interestingly, patients with acute myocardial infarction, especially in association with cardiogenic shock, may have quite high levels of PSA, probably due to prostate ischemia [209, 210].

The availability of ultrasensitive assays to measure PSA has enabled its detection in women's serum at very low concentrations – in most cases below 0.04 ng/mL [211], still the levels may be slightly higher in pregnant women [212]. Interestingly, Aksoy et al. [213] observed that serum PSA levels vary over the course of the menstrual cycle, with slightly lower concentrations during the first days of the follicular phase and during the luteal phase. In any case, PSA of extraprostatic origin does not seem to have any impact on patients treated with radical prostatectomy [214].

The presence of PSA in non-prostate tissues was described in 1994 by Yu and Diamandis et al. [215], who identified it in breast cancer tissue. In this context, PSA expression is related to a better prognosis of the disease [216]. Subsequently, the presence of PSA has also been shown in samples of different origins, including the breast secretion of lactating and non-lactating women, amniotic fluid, breast cysts and bronchoalveolar lavage, as well as in various tumors ranging from colon to kidney [217, 218]. Finally, it should be noted that in women, serum PSA levels are related to androgenic activity [219]. For example, patients with polycystic ovary syndrome present high levels of PSA and its fractions, which may therefore have some clinical value [220, 221].

20. Protein S-100 (S-100)

S-100 is a dimeric protein with low molar mass that belongs to the family of calcium-binding proteins. It is mainly synthesized by astroglial cells and melanocytes. The liver and kidneys are the

main elimination pathways for S-100, making diseases affecting these organs a common cause of false positive results. Elevations in the S-100 concentration have been reported in 46% of patients with kidney failure, in some cases even reaching values 20 times above the URL. It has been observed that 63% of patients with cirrhosis of the liver present protein S-100 concentrations above the URL, even though the majority of patients presented values not exceeding this limit by 2.5 times, and the highest value did not surpass it by more than 3.5 times [222].

Udé et al. [223] described moderate increases in patients with infectious diseases, both with and without cerebral involvement, although the highest values and largest percentage of false positives occured in patients with cerebral involvement. Increases in S-100 concentration have also been described in patients with cerebral lesions with necrosis due to traumatic processes, as well as in cases of ischemic or hemorrhagic stroke [224] and other neurological diseases, such as migraine [225], status epilepticus [226] and brain injury after cardiac surgery [227].

Finally, in patients with systemic lupus erythematosus and neuropsychiatric involvement, S-100 concentrations were found to be two or three times above the URL [228].

21. Squamous cell carcinoma antigen (SCCA)

SCCA belongs to the ovalbumin-serpine family and has been widely used as a TM, specifically for squamous cell carcinoma [229]. SCCA exists in two isoforms, SCCA1 and SCCA2, which have an amino acid similarity of 91%. However, these two isoforms have different specificities toward proteins: SCCA1 inhibits LA papain-like cysteine proteases (cathepsins L, S, and K), while SCCA2 inhibits chemitrypsin-like serine proteases, cathepsin G and chymase [230]. SCCA is extensively expressed in various organs, including tongue, tonsils, esophagus, cervix, vagina, the airways, and skin, as well as the spinous and granular layers of the normal squamous epithelium [229, 230]. The main false positives are associated with chronic kidney disease and dermatological diseases [231]. In obstructive pulmonary disease rates of false positives can range from 15% to 40%, with maximum values close to the URL although usually below 4 ng/mL [95]. A slight increase in SCCA values has been observed in 65% of patients with tuberculosis [3], and similar increases have also been reported in 4% of patients with sleep apnea syndrome [3].

Elevated SCCA concentrations have been reported in 43% to 47% of patients with kidney failure who are not undergoing hemodialysis (with mean concentrations nearly twice the URL). In some cases, maximum values between seven and ten times above the URL have been found, reaching as high as 29 ng/mL [3, 95, 232]. The percentage of false positives in patients treated with hemodialysis ranges from 72% to 77%, but varies depending on the type of membrane used; patients dialysed with cellulose membranes have a false positive rate of 98%, while those dialysed with synthetic membranes have a rate of 76% [5, 232]. In dermatological diseases, concentrations above the URL have been described in patients with psoriasis, eczema, pemphigus, epidermis, erythroderma and atopic dermatitis [95, 230, 231]. Moreover, in most of these diseases, there is a correlation between SCCA concentrations, which may be ten times above the URL, and the surface of the affected skin [230, 231].

22. Thyroglobulin (Tg)

This high molar mass protein is rich in tyrosine and is synthesized by the thyroid follicular cells. Tg concentrations are extremely high in cord blood and plasma of babies, and fall progressively with age [233]. Increases in the Tg concentration above the URL are observed in the third trimester of pregnancy and in various medical conditions, such as Graves' disease, sub-acute thyroiditis, toxic adenoma, and infiltrations of the thyroid by other malignant tumors [234–236]. Heterophile antibodies can also affect

the measurement of Tg (increasing or reducing the concentration measured) in a significant number of patients [237]. Astarita et al. [238] reported Tg false positive results induced by rheumatoid factor.

The correct interpretation of the values obtained for this marker must consider that the presence of circulating anti-thyroglobulin autoantibodies could interfere with the measurement of Tg concentration in some measuring systems, depending on whether the measurement principle is competitive [239] or non-competitive immunoanalysis [240, 241]. Therefore, the anti-thyroglobulin autoantibody concentration should be measured in conjunction with the Tg concentration during follow-up of patients with differentiated thyroid cancer [242]. Anti-thyroglobulin autoantibodies are accepted as a surrogate marker in the follow-up of patients with differentiated thyroid cancer [243]. Ogrin et al. [244] reported elevated anti-thyroglobulin autoantibodies due to an exogenous source in a patient with thyroid cancer who was administered subcutaneous immunoglobulin (Ig). When interpreting serologic tests, it is crucial to take into account whether the patient is receiving Ig replacement therapy.

23. Discussion

A wide variety of iatrogenic, methodological, physiological and pathophysiological processes have been described that increase serum/plasma tumor markers. In some cases, these processes can be identified using laboratory and clinical tests, which may raise the suspicion of false positives. For a correct interpretation of tumor markers, it is essential to be aware of the pathophysiological and pathological situations that can increase their concentrations. This knowledge alerts physicians to the possible presence of false positives if they continue to use conventional discriminant values, such as the upper limit of the reference interval. In studies comprising more than 10,000 patients, Molina et al. [232, 245] identified the causes of false positives and proposed different discriminant values linked to specific clinical situations. For example, for CA19-9 they suggest a discriminant value of 200 U/mL for most pathological and iatrogenic processes, including gastroenteritis, non-severe pulmonary disease and other pathologies with moderate increases; a second value of 500 U/mL for liver disease without biliary tract obstruction, and a third value of 1,000 U/mL which for patients presenting biliary tract alterations, obstructions or infections. The results obtained should be taken into account in studies using serum biomarkers to aid in the diagnosis of a neoplasm, the prognosis of a tumor or the evaluation of treatment. Some comorbidities should be considered as exclusion criteria or different cut-offs should be used to avoid errors in the interpretation of these tumor markers, e.g. patients whose renal function deteriorates during follow-up should be excluded from the study or a higher cut-off or increment should be used to avoid changing the reliability of the study, especially for markers such as HE4, SCC, S-100 and CYFRA 21-1. Diagnostic and prognostic evaluation studies should also exclude patients with such conditions, e.g., CA15-3 in patients with cobalamin deficiency; HE4, SCC, S-100 and CYFRA 21-1 in patients with renal failure; CA19-9 in patients with jaundice; or CA15-3, CA19-9, CEA, CYFRA 21-1 in liver diseases; SCC, S-100 and CYFRA 21-1 in dermatological diseases. On the other hand, depending on the tumor marker, different cut-off points could be used according to pathology, as described for CA19-9. Table 2 shows the considerations that allow a correct interpretation of TMs in clinical practice. The recommendations described can help to improve their interpretation on a personalized basis, considering the patient's clinical context. This approach can thereby improve the diagnostic capacity, follow-up, and prognosis of patients with cancer.

24. Conclusions

The use of tumor markers requires a thorough knowledge of the pathophysiological and iatrogenic conditions that may alter their concentrations in the absence of neoplasia. When using TMs, either in

Table 2
Recommendations for improving the interpretation of the results of tumor marker concentrations and for preventing the diagnostic errors deriving from false positives. These recommendations will be of use in the diagnosis, prognosis, and follow-up of cancer patients

1. A thorough understanding of the patient's condition: for example, certain prostate manipulations can increase PSA, and treatment with ibuprofen is associated with an increase in CA 72-4 levels.
2. Pre-analytical factors: parameters in which the temperature or time up to centrifugation may be critical (e.g. free PSA, ProGRP) and others, as well as sample hemolysis; may increase NSE. The result should be rejected or adjusted according to the formulas [246].
3. Establishment of the specificity of the measuring equipment used. We must be aware of cross-reactivity with other molecules similar to those being tested: for example, between neuron-specific enolase and other enolase isoenzymes.
4. Interference in the detection of heterophile antibody. The following strategy is recommended:
i. Repeat the analysis using another method, preferably using antibodies from another animal.
ii. Perform a heterophile antibody blocking test [247].
iii. Perform different dilutions of the sample and check that the results of the dilutions are proportional.
iv. Determine the concentration of the tumor marker in urine if the molecule is eliminated by this route (e.g., β-hCG), and compare it with the concentration in plasma.
5. Identification of false positives caused by impaired metabolism of tumor marker clearance by using other biological indicators of liver or kidney function: e.g., bilirubin > 3 mg/dL, creatinine 1.5 mg/dL, γGT, urine albumin. if possible, establish a cut-off point for clinical condition to improve interpretation.
6. Use of various biological variables to identify benign diseases that may raise the concentration of a tumor marker in the absence of cancer. For example, cobalamin deficiency may increase the concentration of CA 15-3 antigens.
7. Study of the usefulness of tumor markers after cardiorespiratory arrest; in some cases, NSE, S100 and PSA may indicate hypoxia-related lesions rather than the presence of cancer.
8. Use of evaluative control in order to identify false positives by observing the increase or decrease in two consecutive measurements of the tumor marker concentration over a period of 3-4 weeks. If there is no increase, or if it is below the limits of biological variation established for each marker in the *guidelines* [95], it may be a false positive.
9. Reporting of diseases that may increase tumor marker concentrations in the absence of cancer. For example, the presence of effusions, treatment with NSAIDs or other drugs, SARS-Cov2 infection, dermatological diseases.

the follow-up of a cancer patient or as an aid to diagnosis, a global assessment of the patient is essential in order to take into consideration factors that may alter TM concentrations, applying individualized, clinically adjusted discriminant values.

Author contributions

All authors contributed equally to this work.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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