Review

Can conventional clinical chemistry tests help doctors in the monitoring of oncology patients?

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Abstract: The use of laboratory assays in the diagnostic care of oncology patients can markedly increase the efficacy of cancer treatments. Many cancer-specific biomarker assays have been developed. However, the use of these has some limitations due to their cost. Moreover, not every diagnostic laboratory can perform a complete set of these assays. On the other hand, the smart use of conventional clinical chemistry tests could improve the management of cancer. They could be especially valuable tools in the long-term care of patients with a verified diagnosis. In this review, we discuss the utilization of the conventional clinical chemistry assays for the diagnosis, monitoring and prognosis of various oncological diseases. The use of conventional blood tests to assess the levels of chemical elements, metabolites and proteins (including enzymatic activity measurements) in the care of oncology patients is discussed. We have shown that some clinical chemistry assays could be used in the management of distinct kinds of cancer.

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Introduction

Cancer is one of the leading causes of mortality worldwide. Moreover, the numbers of newly diagnosed cancer cases are twice that of annual cancer mortality rates [1]. The effectiveness of cancer treatment significantly depends on early diagnosis and on the precise verification of a cancer type. There are several approaches to cancer diagnostics. These include various types of instrumental and laboratory diagnostics. Cytomorphologic analysis, flow cytometry [2], circulating tumour cells detection [3, 4], molecular-genetic methods [5, 6] and detection of specific tumour biomarkers [7, 8] are widely used for the laboratory diagnosis of cancer. After diagnosis verification, diagnostic techniques could be used to monitor the effectiveness of treatment and to achieve stable remission. Another important purpose of laboratory diagnosis is to predict the course of the disease (i.e., the risk of mortality) and the development of complications, and to monitor the patient's condition after remission for early detection of cancer recurrence. Laboratory monitoring and prognosis could be performed by specific tumour biomarker assays [8, 9]. The disadvantage of the tumour-specific tests is the relatively high cost. Additionally, not every diagnostic laboratory can perform a complete set of these assays.

On the other hand, tumour development causes marked alterations in body metabolism, hence, cancer can be associated with abnormal results in some clinical chemistry tests. Although conventional clinical chemistry tests have insufficient sensitivity and specificity for cancer diagnosis they can be used in the monitoring and prognosis of a patient's state if an oncological diagnosis has been verified. As conventional clinical chemistry tests are widely available and inexpensive, they can help the physician in the care of cancer patients, especially in developing countries.

In this review, we have set out to summarize current knowledge about the opportunities of the conventional biochemical test's use in oncological clinical practice.

Routine clinical chemistry tests in cancer care

Routine clinical chemistry tests have limited use in the management of oncological patients due to the relatively low specificity and selectivity in the diagnosis of cancer. On the other hand, metabolism alterations associated with tumour development or cancer complications can influence the results of conventional clinical chemistry blood tests. Hence conventional laboratory assays could be applied to assess the severity of disease or its complications. Further normalization of these routine laboratory tests during cancer treatment can be used to monitor the success of therapy. Availability, low cost and low labour intensity of conventional biochemical tests can reduce costs and improve the efficiency of monitoring the effectiveness of therapy compared to the measurement of tumour markers or the use of cytological methods. In the following, we present combined data about the state of the art for conventional clinical chemistry tests

used in predicting changes in the course of cancer development and monitoring the effectivity of treatment.

Assays of elements

Calcium

Alterations of calcium metabolism are common metabolic disorders in the tumour process. Moreover, untreated hypercalcaemia or hypocalcaemia can be dangerous for patients with cancer. Accordingly, the determination of calcium content in blood plasma/serum should be recommended to all patients with neoplasms. The determination of total calcium, adjusted for serum albumin, is considered to be more appropriate in cancer patients than the determination of ionized calcium. It should be noted that hypercalcaemia in cancer patients is found more frequently than hypocalcaemia [10].

Hypercalcaemia is a reasonably common condition in patients with neoplastic processes and occurs in 5-30% of cases, but its prevalence has been progressively decreasing in recent years due to earlier and more effective treatment [10-13]. The most evident causes of hypercalcaemia are associated with osteolytic bone primary tumour metastases [12, 14]. Hypercalcaemia can develop due to the production of parathyroid hormone (PTH) or similar proteins by the tumour [12]. Other causes of hypercalcaemia are disorders of urine calcium excretion due to kidney tumour development or dehydration, often associated with cancer. Another non-specific cause of hypercalcaemia is an alteration of bone metabolism as a result of the cancer patient's low motor activity. In addition to osteolytic bone tumours hypercalcaemia is most often associated with tumours of lung, breast, head and neck, gastrointestinal tract, kidneys, as well as myelo- and lymphoproliferative diseases [10, 11, 13, 15]. However, in 31% of hospitalized cancer patients, hypercalcaemia development is not related to tumours [16]. Measurement of the total calcium concentration in the blood serum in combination with phosphorus, creatinine, PTH, PTH-like peptide and various forms of vitamin D should be recommended to accurately determine the cause of hypercalcaemia [12, 15, 17].

The detection of hypercalcaemia is most important in cases of primary osteogenic tumours or metastases in bone tissue since the degree of increase in calcium concentration can be correlated with the scale of lesion or tumour growth rate. The effect of inhibition of bone resorption in antitumour treatment can be estimated by the rate of normalization of calcium concentration in the blood serum [12, 17]. The increased calcium content of the serum at the time of non-bone cancer diagnosis is associated with a high risk of subsequent detection of bone metastases [18-20]. In various types of solid tumours, hypercalcaemia is a poor prognostic feature associated with a short survival period, especially when combined with a low serum albumin content [21-24]. Suitable treatment of the cancer-associated hypercalcaemia can significantly increase median survival time, for example, from 106 to 432 days in gynaecological cancer patients [25]. Jin et al. noted that development of the cancer-associated PTH-mediated hypercalcaemia within 70 days after a cancer diagnosis significantly increased the risk of shorter survival time in both solid tumour and haematological cancers [26].

Hypocalcaemia occurs in more than 10% of hospitalized cancer patients, with prevalence varying from 1.6 to 13% in different groups of cancer patients [27] and even to 30% in patients with advanced prostate cancer [10]. According to Schattner et al. there are 12 mechanisms that can lead to a decrease in the total calcium content in the serum of patients with malignant tumours [27]. When hypocalcaemia is detected, it is necessary to differentiate between true hypocalcaemia and pseudohypocalcaemia that occurs as a result of reduced serum albumin content, which is often observed in cancer patients [28]. A very rare cause of pseudohypocalcaemia is the impact on the results of calcium determination on some paramagnetic contrast agents for magnetic resonance tomography [29, 30]. True hypocalcaemia can be observed both at normal or low concentrations of PTH in the blood serum and at its elevated content. One of the causes of hypocalcaemia is a magnesium deficiency that causes resistance of cells to the action of PTH with subsequent violation of PTH secretion by parathyroid glands. Another reason is the destruction of parathyroid glands tissue (or their removal) with the development of partial or complete PTH deficiency in the body. In tumour processes, a combination of hypocalcaemia with elevated PTH level in the blood serum as a result of secondary hyperparathyroidism is more often observed. In this situation, the causes of hypocalcaemia are ectopic production of calcitonin by tumours, vitamin D deficiency, calcium malabsorption due to the development of tumours or acute pancreatitis (which can occur as a response to prior hypercalcaemia), excessive deposition of calcium in osteoblastic metastases or as a consequence of acute hyperphosphatemia (which usually occurs with massive destruction of cells, including tumour lysis syndrome), or excessive calcium secretion due to disorders of kidney function [27]. A decrease in the level of circulating calcium may also occur due to the use of some anticancer drugs or bone resorption inhibitors [10, 31, 32].

The prognostic value of hypocalcaemia in cancer has not been systematically investigated, but apparently can significantly depend on the cause of its occurrence. In many cases, hypocalcaemia is transient and asymptomatic or with mild symptoms. Hypocalcaemia may have prognostic value in patients with acute and urgent conditions and in monitoring the effectiveness of tumour treatment. Hypocalcaemia has important diagnostic and prognostic value in osteoblastic metastases of tumours in bone tissue [33, 34]. To identify the cause of hypocalcaemia in cancer, it is recommended to use a complex of conventional biochemical tests, including the determination of total serum calcium, magnesium, PTH, creatinine, phosphate, liver enzymes, amylase and 25-hydroxide vitamin D [27].

Phosphorus (Phosphate)

Changes in the content of serum phosphorus (in the form of inorganic phosphates) occur in cancer patients much less often than hypercalcaemia or hypocalcaemia. However, hypo- or hyperphosphatemia can often threaten a patient's life. Osteolytic bone tumours (primary and metastases) and onco-hematologic diseases (e.g. multiple myeloma) may be accompanied by hyperphosphatemia [35]. An increase in serum phosphorus level can be observed as a result of tumour treatment [36-38]. A significant increase in serum phosphorus after tumour removal is a poor prognostic factor for patient survival [38]. Often, hyperphosphatemia is a typical sign of tumour lysis syndrome [39-42] and was proposed as one of the criteria of the laboratory tumour lysis syndrome diagnosis [43]. Since the development of tumour lysis syndrome threatens the patient's life due to the possible development of complications (acute renal failure, cardiac

arrhythmia, convulsions, and multiple organ damage), the presence and severity of hyperphosphatemia (along with the content of creatinine and uric acid) can be an important prognostic factor [42, 44, 45]. Moreover, the elevation of serum phosphate concentration higher than its upper normal limit (UNL) can transform an intermediate (1% to 5%) risk of tumour lysis syndrome development into a high (greater than 5%) risk in various lymphoproliferative disorders [41]. Hyperphosphatemia is a poor survival prognostic factor after surgical removal of colorectal tumours [38]. Detection of hyperphosphatemia is important for determining the cause of tumour-associated hypocalcaemia [27].

The reduction of serum phosphorus associated with the development of tumours is quite rare, and can be associated with the paraneoplastic syndrome of tumour-induced osteomalacia, leading to increased renal phosphate excretion [46-49], with the development of osteoblastic metastasis in bone tissue [50-52], and is also sometimes observed in lymphoproliferative diseases [53]. Some anti-cancer drugs can lead to a reduced phosphorus level in the blood serum [54].

Iron

Oncological diseases are often accompanied by the development of anaemia (prevalence up to 64% among cancer patients), while in many cases it is secondary to iron deficiency [55, 56]. The main mechanism of development is the increased production of interleukin (IL)-6, which activates the secretion of hepcidin. This leads to the retention of iron in the depot and suppression of its release into the bloodstream. At the same time, there is a higher degree of transferrin serum iron saturation [55, 57, 58]. Therefore, the determination of the level of latent iron-binding capacity or ferritin concentration is a more accurate indicator of iron deficiency in cancer than the content of iron in the blood serum [58-61].

Assays of metabolites
Glucose

Glucose determination is one of the most widely used biochemical tests. In oncology, it is used to detect hypoglycemia, which often accompanies the tumour process. Several factors can lead to a decrease in blood glucose level. First is the ability of some tumours to secrete insulin or other carbohydrate metabolism regulators: glucagon-like peptide, insulin-like growth factors and somatostatin. They are tumours originating from the islet cells or cells of APUD-system (e.g., stromal tumours of the gastrointestinal tract). Another cause of hypoglycemia is high glucose consumption by large, aggressive or rapidly growing tumours. Therefore, the normalization of glucose level during treatment can serve as a good criterion for therapy effectiveness [45, 62]. Blood plasma/serum glucose concentration can be used to predict remission period and overall survival in some kinds of cancer [63-67].

Uric acid

The determination of uric acid content is another routine analysis that can be useful in monitoring the progression of cancer and making decisions about treatment. Approximately 20% of patients with lympho- and myeloproliferative diseases have hyperuricemia. Excess production of uric acid is associated with extremely rapid production and destruction of blood cells and hypermetabolism syndrome [68]. Severe hyperuricemia is observed as a result of tumour lysis [69], which allows the use of the uric acid levels in the blood serum to assess the risk of tumour lysis syndrome [41, 70, 71], and for the monitoring of the patient's life-threatening condition [42, 45]. In colorectal tumours, hyperuricemia is an indicator of the risk of cancer-associated metabolic syndrome [72], and the normalization of uric acid level can be used in the monitoring of therapy effectiveness [73].

Bilirubin

A recent study has shown that an elevated level of total serum bilirubin in intrahepatic cholangiocarcinoma is an independent predictor of negative prognosis [74]. However, higher bilirubin content is a factor indicating a reduced risk of patient's death in various types of cancer [75, 76] and a protective factor for colorectal cancer [77, 78]. Elevated levels of total bilirubin in the serum also can play a protective role in non-liver cancers [79]. Higher direct bilirubin concentrations have been shown as a predictor of lymph node metastasis in rectal cancer [80].

Creatinine

Elevated concentration of creatinine is a strong predictor of tumour lysis syndrome development in patients with haematological malignancies [71] and is recommended to use in the grading of clinical tumour lysis syndrome [43].

Assays of enzymes
Hepatic enzymes

Among the usual biochemical tests based on determining the activity of enzymes in blood serum or plasma, a special place belongs to the so-called hepatic enzymes. It is well known that increased activity of enzymes such as alanine aminotransferase (ALT), aspartate transferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) is observed in the destruction of liver parenchyma cells, regardless of their cause [81]. Therefore, an increase in the level of hepatic enzymes in an established oncological diagnosis will serve as an indicator of the degree of liver damage. Accordingly, a decrease in the activity of these enzymes during treatment will indicate its effectiveness. The same indicators are important for the prognosis of the disease. Thus, an increase in the activity of any aminotransferase above 80 U/L, especially with hypoalbuminemia indicates a high death risk of patients with tumours at late stages of development [82]. Adverse prognostic factors in the survival of patients with intrahepatic cholangiocarcinoma are increased activities of GGT and ALP [74].

Alkaline phosphatase

Alkaline phosphatase (ALP) is a body-wide expressed enzyme. As ALP is essentially involved in bone formation and secreted by osteoblasts [83], determination of its activity is widely used in laboratory diagnostics of bone tumours [84]. Although this test is often used to detect metastases of other bone tumours [85, 86], its prognostic value is relatively low [87], and the positive test result is associated primarily with osteoblastic metastases [84]. A comparison of patients with osteosarcoma and patients with other lesions of bone tissue showed that the determination of ALP

activity has a high specificity (about 90%) in the detection of primary osteogenic sarcoma, but the sensitivity of this test was relatively small (about 53%). ALP activity in the serum is linearly correlated with tumour size [88].

The relatively low specificity of ALP activity determination in other tumour processes in bone tissue is associated with peculiarities of this enzyme biology. There are four ALP isoforms in the human body: tissue-non-specific (encoding by ALPL gene), intestinal (encoding by ALPI gene), placental (encoding by ALPP gene), and placental-like (encoding by ALPPL2 gene). The last three isoforms are closely homological to each other, and their expression is specific to particular tissues. Tissue-non-specific ALP is expressed in different organs, mainly in liver, bone and kidney [83]. Therefore, an increase in the total ALP activity in blood serum/plasma can occur due to the release of the enzyme from almost any tissue. In particular, the increase in the ALP activity in blood serum may be due to the lesions of liver tissue mentioned above. Moreover, tests to determine bone-specific ALP also do not differentiate enzyme molecules originating from bone, liver, kidney or, for example, nervous tissue. Improved diagnosis of tumours using the ALP assay is possible by combination with other biomarkers, for example, metalloproteinase MMP-9 [89] or determination of tissue-specific ALP isoforms [90]. However, such tests are not commonly used in laboratory medicine.

At the same time, the determination of total ALP activity can be used as a biomarker for monitoring or in the prognosis of patients with an already verified cancer pathology. The high serum ALP activity in bone metastases of various tumours is correlated with shorter survival of patients [91]. Moreover, if the activity of ALP exceeds a certain critical level (non-equal for various types of cancer) at the time of initial cancer diagnosis, this may indicate a high risk of metastasis in bone tissue even if specific tumour biomarkers have no predictive significance [18, 20, 92-94]. Diagnostic accuracy of bone metastases prediction can be improved by the use of a combination of the useful laboratory tests: ALP + calcium + hemoglobin in bladder cancer [20] and in renal cancer [93]; ALP + the prostate-specific antigen (PSA) [92, 95] or ALP + PSA + tartrate-resistant acid phosphatase in prostate cancer [96]. The high activity of ALP in the blood serum is associated with poor survival prognosis and a high risk of metastasis in patients with osteosarcoma [88, 97]. The specificity of osteosarcoma metastases prediction during the next 3 years is 90% with a sensitivity of about 53%. The decrease in the ALP activity during treatment of osteosarcoma may serve as an indicator of the treatment effectiveness [88]. On the other hand, some studies found no relation between bone metastases formation and elevated serum ALP activity [98].

Serum ALP activity was shown to predict overall survival rates of prostate cancer patients during docetaxel treatment (especially in combination with PSA and C-reactive protein levels) and the safety of longer docetaxel therapy (better in combination with haemoglobin concentration) [98]. ALP was also proposed as a biomarker to differentiate transient PSA rise after the initiation of chemotherapy (PSA flare) from early progressive PSA elevation in prostate cancer patients with bone metastasis. Absence of elevation of ALP during the first cycle of docetaxel chemotherapy in patients with castrate-resistant prostate cancer was closely associated with transient PSA flare [100].

Additionally, ALP determination has specific significance in some cases of cancer-associated hypercalcaemia. Patients with lung cancer-associated hypercalcaemia had a poorer survival prognosis in the case of normal ALP levels compared to patients who had elevated ALP levels [24].

Acid phosphatase

Human acid phosphatase (ACP) has more isoforms than the ALP [101]. In the laboratory diagnosis of cancer, the most important isoforms are prostatic acid phosphatase (PAP or PACP, encoded by ACP3 gene) and tartrate-resistant acid phosphatase (TRACP, encoded by ACP5 gene).

PACP has historically been the first biomarker used in prostate cancer diagnosis since the 1940s. With the introduction into clinical practice of the PSA test, application of PACP assay in the diagnosis of prostate cancer gradually subsided due to its low sensitivity, especially in the early stages [102, 103]. Although intracellular and secretory PACP in large quantities is synthesized in normal and transformed epithelial cells of the prostate gland [103], in highly differentiated tumours the synthesis of this enzyme is reduced [103, 104]. In extra-prostatic cells, PACP is synthesized mainly in the form of a transmembrane variant (alternative splicing product), and the synthesis of cytosolic variant is insignificant or absent [104]. Importantly, tumours localized not only in the prostate gland can synthesize and secrete PACP [103]. All these facts caused a decrease of interest in the use of PACP for the diagnosis of prostate cancer. However, in recent years, PACP assay has again been used as a diagnostic and monitoring test: to predict the risk of relapse after surgery or radiotherapy and to predict survival [102] and to estimate the risk of bone metastases [96]. It was shown that the metastases of prostate tumours in bone tissue express PACP [105] regardless of whether the metastases are osteoblast or osteoclast [106]. Subsequent studies may be able to evaluate the significance of PACP assay in the prognosis and monitoring of metastatic prostate cancer.

TRACP is an isoform of acid phosphatase, which is easily enzymologically identified because TRACP activity is not inhibited by L-tartrate. This enzyme can be synthesized in two variants, denoted as isoforms 5a (TRACP-5a) and 5b (TRACP-5b). TRACP expression is detected in various cell types including osteoclasts, neurons, adipocytes and activated macrophages [107]. Activated osteoclasts synthesize and secrete large amounts of TRACP, so the determination of the activity or amount of this enzyme has long been widely used in the diagnosis of various bone lesions, including primary tumours and bone metastases [84, 96, 108]. However, the increase in the activity of TRACP in the blood serum can also be observed in non-oncological diseases, such as obesity [109] or rheumatoid arthritis [110]. Because isoform 5b is specific to osteoclasts, but not to other types of human cells [84, 111], it is recommended to use the definition of TRACP-5b for a more accurate diagnosis of bone metastases [84, 87, 91]. However, for prognostic purposes and to monitor treatment response in patients with an established diagnosis it is sufficient only to assess total levels of serum TRACP activity [108]. Determination of the activities of TRACP and ALP allows detecting and monitoring of both osteoclastic and osteoblastic bone tumours [96].

Lactate dehydrogenase

Data about the prognostic significance of increased serum activity of lactate dehydrogenase (LDH) are contradictory. Some studies found an association of elevated LDH activity with a very poor prognosis [76, 112] but other studies did not [22, 75, 99,

113]. A meta-analysis of 76 studies showed increased LDH levels (median cut-off 245 U/L) were associated with increased risk of shorter survival time especially in renal cell, melanoma, gastric, prostate, nasopharyngeal and lung cancers [114]. In various lymphoproliferative disorders LDH activity (cut-off is 2×UNL) is used to differentiate low, intermediate and high risk of tumour lysis syndrome development [41, 69]. Serum LDH activity higher than 500 U/L was strongly associated with developed tumour lysis syndrome in pediatric patients with Burkitt's lymphoma or B-cell acute lymphoblastic leukaemia [115]. Many studies identified high LDH activity as an independent risk factor for tumour lysis syndrome [44, 70, 71, 116].

Assays of non-enzymatic proteins
Acute phase proteins

Acute phase proteins (APPs) are blood plasma proteins whose concentration can change during inflammation response development. Synthesis and secretion of APPs by hepatocytes and some extrahepatic cells are regulated by proinflammatory cytokines such as IL-1, IL-2 and tumour necrosis factor-α (TNFα). One of the most important and well-known APPs is C-reactive protein (CRP) [117, 118].

The increase in the content of positive proteins of the acute phase of inflammation is observed in tumours of various types. Theoretically, changes in these indicators can be used to monitor the course and treatment effectiveness in various types of extrahepatic cancer [117]. It is known that APPs as biomarkers usually have high sensitivity (but low specificity) [118]. However, a small number of large clinical trials have been conducted. An especially important indicator today is the content of C3 and C4 complement proteins. This is due to the peculiarities of the relationship between the complement system and the tumour process. Complement activation often stimulates tumour growth, causing tumour cells dedifferentiation. This can increase cancer's aggressiveness as well as promote metastasis. Moreover, some tumour cells secrete several complement proteins, as well as expressing on their surface anaphylatoxin receptors involved in the activation of tumour growth. Thus, the determination of C4 and – especially – C3 proteins levels can serve as an indicator of aggressiveness and metastatic activity of tumours [119, 120, 121]. Other APPs can also be used to predict the progression of tumour growth and metastasis, to assess the risk of death, and to monitor the effectiveness of treatment. Thus, the level of haptoglobin can be used to predict the rate of progression and the risk of tumour metastasis [122-124]. Determination of α1-antitrypsin in the blood serum is a good indicator for monitoring the effectiveness of anticancer therapy [125, 126]. The increase in CRP level in cancer patients is independently associated with a decline in quality of life (for women with breast cancer) [127], increased risk of cancer-related mortality (for men with lung cancer) [128], elevated lethality (for patients with gastric cancer after gastrectomy) [61] and poor overall survival during docetaxel treatment of patients with prostate cancer [99].

Beta-2-microglobulin

Another often recommended analysis for cancer patients is the determination of β2-microglobulin. Its increased content is observed in carcinomas, solid tumours of lungs, kidneys, prostate, breast, lympho- and myeloproliferative diseases. This protein is associated with stimulation of various tumour growths, so its

increase can serve as a good indicator for assessing the rate of tumour progression, and the normalization of its content will be a criterion for the treatment effectiveness [129, 130].

Serum albumin

Hypoalbuminemia can accompany a variety of cancers. In patients with tumours in the late stages of development, hypoalbuminemia is a strong negative predictor: a decrease in serum albumin content below 30 g/L is associated with a twofold increase in the risk of death of a patient in the next six months [82]. The decrease in albumin level in colorectal tumours, prostate cancer, breast cancer, liver tumours also indicates an unfavourable medium-term prognosis [74, 76, 131, 132]. Hypoalbuminemia is a predictor of poor survival in cancer-associated hypercalcaemia [21, 22, 133-135]. At the same time, it should be remembered that in cancer patients, the development of hypoalbuminemia may be associated not only with impaired liver function or changes in the distribution of albumin in the body but also with the development of complications of the underlying disease, for example, chronic renal failure.

Proteins associated with the thyroid gland

Two indicators related to the function of thyroid gland can be used for the differential diagnosis of thyroid carcinoma. This possibility is based on the increase in the content of calcitonin in most patients with medullary carcinoma (it is preferable to conduct the test with stimulation) [136] and increased serum level of thyroglobulin in patients with other types of thyroid carcinoma [137].

Summary

Appendix 1 summarises data from the research publications estimating the significance of routine blood serum/plasma clinical chemistry tests in cancer patient care.

Conclusion

The modern clinical diagnostic laboratory has a large set of diagnostic tests; however, their potential is not fully used. Even routine biochemical tests can significantly improve patient management. Thus, our review clearly shows that several routine biochemical laboratory tests used in the case of certain types of cancer to solve specific diagnostic problems can help to determine the best clinical decisions for cancer patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix 1. Summary of clinical studies estimating the significance of routine blood serum/plasma clinical chemistry tests in cancer patient care.

Disease / syndrome	Reference	No. of patients	Type of assessment	Clinical chemistry test	Positive test values / goal value	Outcome / results / recommendation
General population	[128]	33567	Prognosis	CRP	≥ 3 mg/L	Predictor of cancer-related mortality in men, HR = 1.25-2.07 (95%CI) No influence on cancer-related mortality in women, HR = 0.75-2.06 (95%CI)
Acute lymphoblastic leukaemia	[138]	60	Prognosis	LDH	> 1000 U/L	Predictor of TLS, OR = 1.2-20.9 (95%CI)
Acute lymphoblastic leukaemia	[139]	160	Prognosis	LDH	> 2000 U/L	Predictor of TLS, OR = 1.52-9.89 (95%CI)
Acute lymphoblastic leukaemia	[116]	328	Prognosis	LDH	> 2000 U/L	Predictor of TLS, OR = 4.0-14.7 (95%CI)
Acute lymphocytic leukaemia	[63]	278	Prognosis Recurrence monitoring	Glucose Glucose	≥ 11.1 mM ≥ 11.1 mM	Predictor of shorter survival, HR = 1.221-2.411 (95%CI) Predictor of recurrence risk, HR = 1.132-2.179 (95%CI)
Acute myeloid leukaemia	[65]	283	Prognosis	Glucose	> 6.1 mM	Predictor of shorter survival, HR = 1.23-1.55 (95%CI)
Acute myeloid leukaemia	[70]	194	Prognosis	Uric acid LDH	> UNL > 1.19 × UNL	Predictor of TLS, OR = 7.26-403.65 (95%CI) Predictor of TLS, OR = 1.42-6.44 (95%CI)
Acute myeloid leukaemia	[71]	772	Prognosis	Creatinine Uric acid LDH	> 123.8 μM > 446 μM 1-4 × UNL > 4 × UNL	Predictor of clinical TLS, OR = 1.6-6.8 (95%CI) Predictor of clinical TLS, OR = 1.5-8.2 (95%CI) Predictor of clinical TLS, OR = 1.3-4.8 (95%CI) Predictor of clinical TLS, OR = 1.7-23.1 (95%CI)
Non-Hodgkin's lymphoma	[115]	1192	Prognosis	LDH	> 500 U/L	High LHD activity and advanced stage of non-Hodgkin's lymphoma are associated with a high risk of TLS development in pediatric patients
Breast cancer	[98]	148	Prognosis	ALP		No relation to the risk of bone metastases
Breast cancer, non-metastatic	[76]	2425	Prognosis	Albumin Protein, total Bilirubin, total ALP ALT AST LDH	> 39 g/L > 69 g/L > 3.42 μM > 79 U/L > 19 U/L > 37 U/L > 469 U/L	Predictor of longer survival, HR = 0.40-0.75 (95%CI) No influence on survival, HR = 0.57-1.81 (95%CI) Predictor of longer survival, HR = 0.45-0.85 (95%CI) No influence on survival, HR = 0.95-1.65 (95%CI) No influence on survival, HR = 0.59-1.04 (95%CI) No influence on survival, HR = 0.91-2.15 (95%CI) Predictor of shorter survival, HR = 1.08-1.88 (95%CI)
Breast cancer	[19]	534	Prognosis	Calcium LDH	> 2.55 mM	Predictor of bone complications, HR = 1.12-1.58 (95%CI) for the time to the first SRE and HR = 1.15-1.51 (95%CI) for SRE frequency No modification of risk of the time to the first SRE and SRE frequency
Lung cancer	[140]	52	Diagnosis of complications	ALP, bone-specific	> 11 U/L	Diagnosis of bone metastases, sensitivity 89%, specificity 44%, ROC-AUC = 0.79
Lung cancer, small cell	[141]	232	Prognosis	ALP	≥ 2×UNL	Predictor of shorter survival, HR = 1.542-7.587 (95%CI)
Lung cancer, non-small cell	[123]	415	Diagnosis Prognosis	Hp Hp	> 1.495 g/L > 1.495 g/L	Sensitivity 63.9%, specificity 88.1%, ROC-AUC = 0.809 Predictor of shorter survival, HR = 1.47-4.49 (95%CI)
Lung cancer	[62]	1548	Prognosis	Glucose	> 7 mM	Predictor of shorter survival, HR = 1.18-1.87 (95%CI)
Lung cancer	[142]	2021	Diagnosis of complications	ALP	not specified by authors	Diagnosis of bone metastases, sensitivity 41.3%, specificity 77.1%, ROC-AUC = 0.610
Ovarian cancer	[66]	199	Prognosis Recurrence monitoring	Glucose Glucose	per 3.89 mM per 3.89 mM	Predictor of shorter survival, HR = 1.07-3.49 (95%CI) Predictor of shorter remission interval, HR = 1.42-4.28 (95%CI)
Cervical cancer	[67]	134	Prognosis Recurrence monitoring	Glucose Glucose	≥ 5.66 mM ≥ 5.66 mM	Predictor of shorter survival, HR = 1.01-6.40 (95%CI) Predictor of shorter progression-free interval, HR = 1.06-3.33 (95%CI)
Prostate cancer	[91]	117	Prognosis Diagnosis of complications	ALP, total ALP, bone-specific ALP, total ALP, bone-specific	> 129 U/L > 15.2 μg/L > 129 U/L > 15.2 μg/L	No influence on survival, RR = 0.10-41.0 (95%CI) No influence on survival, RR = 0.01-20.8 (95%CI) Diagnosis of bone metastases, sensitivity 81%, specificity 93% Diagnosis of bone metastases, sensitivity 75%, specificity 93%
Prostate cancer	[95]	203	Diagnosis of complications	ALP	> 286 U/L	Diagnosis of bone metastases, OR = 1.02±0.003 (M±SE), sensitivity 72.7%, specificity 91.9%, ROC-AUC = 0.87
Prostate cancer	[96]	215	Prognosis	ALP TRACP	> 288 U/L > 10.4 U/L	Predictor of bone metastases, OR = 3.203-26.109 (95%CI) Predictor of bone metastases, OR = 1.009–8.287 (95%CI)
Prostate cancer	[92]	83	Diagnosis of complications	ALP	> 115 U/L	Diagnosis of bone metastases, sensitivity 57.14%, specificity 64.80%, ROC-AUC = 0.736
Prostate cancer with bone metastases	[86]	52	Prognosis	ALP, bone-specific	> 26 μg/L	Predictor of biochemical progression, HR = 2.71-15.62 (95%CI)
Prostate cancer, treatment by docetaxel	[99]	279	Prognosis Treatment effectiveness prediction	ALP CRP LDH ALP CRP LDH	≥ 189 U/L ≥ 3.2 mg/L ≥ 215 U/L ≥ 189 U/L ≥ 3.2 mg/L ≥ 215 U/L	Predictor of shorter survival, HR = 1.04-7.71 (95%CI) Predictor of shorter survival, HR = 1.08-3.55 (95%CI) No influence on survival, HR = 0.68-2.27 (95%CI) Predictor of longer treatment, HR = 0.12-0.54 (95%CI) No influence on therapy duration, HR = 0.35-1.90 (95%CI) No influence on therapy duration, HR = 0.31-1.18 (95%CI)
Prostate cancer, treatment by docetaxel	[100]	83	Prognosis	ALP	Initial decrease after the treatment start	Predictor of transient PSA flare, OR = 1.648-161.558 (95%CI)
Renal cancer	[93]	372	Diagnosis of complications	ALP	> 105.5 U/L	Diagnosis of bone metastases, OR = 1.491-4.020 (95%CI), ROC-AUC = 0.749, sensitivity 57.9%, specificity 83.5%

Disease / syndrome	Reference	No. of patients	Type of assessment	Clinical chemistry test	Positive test values / goal value	Outcome / results / recommendation
				Calcium	> 2.615 mM	Diagnosis of bone metastases, OR = 1.088-4.817 (95%CI), ROC-AUC = 0.633, sensitivity 36.8%, specificity 95.2%
Gastric cancer	[18]	1342	Prognosis	ALP	> 115 U/L	Predictor of bone metastases, OR = 1.10-22.81 (95%CI)
				Calcium, albumin-corrected	> 2.5 mM	Predictor of shorter survival, HR = 1.01-4.95 (95%CI)
Gastric cancer	[62]	3979	Prognosis	Glucose	> 7 mM	Predictor of shorter survival, HR = 1.25-1.84 (95%CI)
Gastric cancer	[61]	429	Prognosis	CRP	≥ 1.5 mg/L	Predictor of shorter survival, HR = 1.064-2.858 (95%CI)
				Albumin	< 39 g/L	Predictor of shorter survival, HR = 1.401-3.518 (95%CI)
				Iron	< 600 µg/L	No influence on survival, HR = 0.879-2.245 (95%CI)
Colorectal cancer	[78]	421	Disease prediction	Bilirubin, total	each 1 µM decrease	7% increase of sporadic colorectal cancer risk
Colorectal cancer	[94]	2790	Diagnosis of complications	ALP	> 85.5 U/L	Diagnosis of bone metastases, OR = 1.004-1.010 (95%CI), sensitivity 81.1%, specificity 71.5%, ROC-AUC = 0.829
Colorectal cancer	[124]	475	Diagnosis of complications	Hp	> 1 mg/L	Diagnosis of liver metastases, sensitivity 63.2%, specificity 54.6%, ROC-AUC = 0.735
Colorectal cancer	[60]	576	Prognosis	Iron	Multiple levels	No influence on survival
Colorectal cancer	[77]	83	Disease prediction	Bilirubin, total	each 17.1 µM decrease	Predictor of decreased risk of colorectal cancer, OR = 0.254-0.260 (95%CI)
Rectal cancer	[80]	469	Prognosis	Bilirubin, direct	> 2.6 µM	Predictor of lymph node metastasis, OR = 1.098-2.338 (95%CI)
Colorectal cancer, after surgical removal	[38]	1241	Prognosis	Phosphate	> 1.4535 mM	Predictor of shorter survival, HR = 1.49-2.29 (95%CI)
Pancreatic cancer	[75]	183	Prognosis	Bilirubin, total	log [bilirubin]	Predictor of shorter survival, HR = 1.43-2.36 (95%CI)
				LDH	log [LDH]	No influence on survival, HR = 0.83-1.75 (95%CI)
				CRP	log [CRP]	Predictor of shorter survival, HR = 1.06-1.63 (95%CI)
Intrahepatic cholangiocarcinoma	[74]	173	Prognosis	Albumin	≥ 40.7 g/L	Predictor of longer survival, HR = 0.466-0.917 (95%CI)
				ALP	≥ 138 U/L	Predictor of shorter survival, HR = 1.290-2.560 (95%CI)
				GGT	≥ 113 U/L	Predictor of shorter survival, HR = 1.281-2.540 (95%CI)
				Bilirubin, total	≥ 12.2 µM	Predictor of shorter survival, HR = 1.198-2.389 (95%CI)
				Bilirubin, direct	≥ 4.7 µM	Predictor of shorter survival, HR = 1.403-2.804 (95%CI)
Bladder cancer	[20]	902	Diagnosis of complications	ALP	> 116 U/L	Diagnosis of bone metastases, OR = 1.004-1.010 (95%CI), ROC-AUC = 0.691, sensitivity 38%, specificity 92.7%
				Calcium	> 2.535 mM	Diagnosis of bone metastases, OR = 3.836-44.384 (95%CI), ROC-AUC = 0.606, sensitivity 32%, specificity 93.5%
Osteosarcoma	[88]	210	Diagnosis	ALP	> 300 U/L (age < 15 years), > 115.5 U/l (age ≥ 15 years)	Sensitivity 53.2%, specificity 90.1%
			Prognosis	ALP		Predictor of shorter survival, HR = 1.07-4.21 (95%CI)
Osteosarcoma	[97]	3228, meta-analysis	Prognosis	ALP		Predictor of shorter survival, HR = 1.61-2.06 (95%CI)
						Predictor of bone metastases, RR = 1.61-9.49 (95%CI)
Carcinomas	[85]	3268, meta-analysis	Diagnosis of complications	ALP, bone-specific		Diagnosis of bone metastases, sensitivity 74%, specificity 80%, ROC-AUC = 0.86
Solid tumours	[114]	22882, meta-analysis	Prognosis	LDH	> 245 U/L (median cut-off)	Predictor of shorter survival, HR = 1.62-1.79 (95%CI)
Cancer, advanced stage	[82]	522	Prognosis	ALT	> 80 U/L	Predictor of death within 2 weeks, OR = 1.01-3.54 (95%CI)
				AST	> 80 U/L	Predictor of death within 2 weeks, OR = 1.18-3.43 (95%CI)
				Albumin	< 30 g/L	Predictor of death within 6 months, OR = 1.27-10.66 (95%CI)
						Predictor of death within 6 months, OR = 1.01-3.88 (95%CI)
Lung cancer-associated hypercalcaemia	[113]	72	Prognosis	Calcium, albumin-corrected	> 2.65 mM	No correlation with median survival time
				Phosphate	not specified by authors	No influence on survival, HR = 0.83-3.94 (95%CI)
				ALP	not specified by authors	Predictor of shorter survival, HR = 1.00-1.03 (95%CI)
				LDH	not specified by authors	No influence on survival, HR = 0.92-1.42 (95%CI)
Cancer-associated hypercalcaemia	[143]	138	Prognosis	Calcium, albumin-corrected	>2.55 mM	Median survival time <2 months
Colorectal cancer-associated humoral hypercalcaemia	[144]	30	Prognosis	Calcium, albumin-corrected		No relation to survival time
Gynaecological cancer-associated hypercalcaemia	[25]	256	Prognosis	Calcium, albumin-corrected	≥ 3.0 mM	Predictor of shorter survival, HR = 2.93-8.40 (95%CI)
					≥ 3.5 mM	Predictor of shorter survival, HR = 5.32-40.05 (95%CI)
Cancer-associated hypercalcaemia	[26]	115	Prognosis	Calcium	> 2.55 mM	Predictor of shorter survival if calcium elevation develops within 70 days after a cancer diagnosis, HR = 1.04-2.47 (95%CI)
Squamous cell carcinoma-associated hypercalcaemia	[22]	220	Prognosis	Calcium, albumin-corrected	≥ 3.0 mM	Predictor of shorter survival, HR = 1.05-2.01 (95%CI)
				Albumin	< 32 g/L	Predictor of shorter survival, HR = 1.07-2.04 (95%CI)
				ALP		No correlation with median survival time

Disease / syndrome	Reference	No. of patients	Type of assessment	Clinical chemistry test	Positive test values / goal value	Outcome / results / recommendation
				LDH		
				CRP		
				Urea		
Lung cancer-associated hypercalcaemia	[24]	64	Prognosis	Calcium, albumin-corrected	≥ 2.90 mM	Median survival time was 14 days at higher levels vs. 186 days at lower levels; HR = 2.968-15.705 (95%CI)
				ALP	< 120 U/L	Median survival time was 36 days at lower levels vs. 182 days at higher levels; HR = 1.082-3.542 (95%CI)
Oral cancer-associated hypercalcaemia	[135]	91	Prognosis	Albumin		Positive correlation with median survival time (r= 0.31)
				Calcium, albumin-corrected		No significant correlation with median survival time (r= –0.09)
Severe cancer-associated hypercalcaemia	[145]	287	Treatment monitoring	Calcium, albumin-corrected	2.70 mM	Goal value during treatment by bisphosphonates
Cancer-associated hypercalcaemia	[21]	252	Prognosis	Calcium, albumin-corrected	> 2.83 mM	Median survival time of patients without squamous cell carcinoma or/and liver metastasis was 797 days if both tests were negative and 49 days if at least one of them was positive
				Albumin	< 34 g/L	
Cancer-associated hypercalcaemia	[133]	126	Prognosis	Calcium		Negative correlation with median survival time (r= –0.39)
				Albumin		Positive correlation with median survival time (r= 0.26)
Solid tumour cancer-associated hypercalcaemia	[134]	306	Prognosis	Albumin	< 25 g/L	No influence on survival, HR = 0.82-2.05 (95%CI)
				CRP	> 30 mg/L	No influence on survival, HR = 0.56-2.65 (95%CI)
Cancer-associated hypercalcaemia	[23]	115	Prognosis	Calcium	> 2.75 mM	Duration of hypercalcaemia > 140 days after a cancer diagnosis is a predictor of shorter survival, HR = 1.417-4.074 (95%CI)
TLS during treatment of haematological cancer	[43]	n.a. (criteria of TLS were noted)	Diagnosis / Treatment monitoring	Uric acid	> 476 µM	Laboratory TLS is diagnosed if 2 or more alterations are observed within 7 days of chemotherapy

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; Hp, haptoglobin; HR, hazard ratio; IU, international units; LDH, lactate dehydrogenase; M±SE, mean ± standard error; n.a., not applicable; OR, odds ratio; PACP, prostatic acid phosphatase; ROC-AUC, area under the receiver operating characteristics (ROC) curve; SRE, skeletal-related event; TLS, tumour lysis syndrome; TRACP, tartrate-resistant acid phosphatase; UNL, upper normal limit.