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ARTN and CCL23 predicted chemosensitivity in acute myeloid leukemia: an Olink® proteomics approach

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Abstract

Background The standard "7 + 3" induction results in 30% of de novo acute myeloid leukemia (AML) patients not achieving complete remission (CR). We aimed to utilize the Olink® platform to compare the bone marrow plasma proteomic profiles of newly diagnosed de novo AML patients who did and did not achieve CR following "7 + 3" induction treatment.

Methods This prospective study included 43 untreated AML patients, stratified into CR ($n = 29$) and non-CR ($n = 14$) groups based on their response to "7 + 3" induction therapy. We employed the Olink® Explore-384 Inflammation platform for proteomic analysis to investigate differences in bone marrow plasma protein levels between the CR and non-CR groups.

Results Proteomic analysis demonstrated that the CR group exhibited significantly higher bone marrow plasma levels of ARTN and CCL23 than did the non-CR group. Immunohistochemical staining confirmed a higher proportion of tissue samples with intense staining for ARTN (25.40% vs. 7.05%, $p = 0.013$) and CCL23 (24.14% vs. 14.29%, $p = 0.039$) in the CR group. These findings were corroborated by bulk-RNA-seq, which indicated significantly elevated mRNA expression levels of ARTN (1.93 vs. -0.09; $p = 0.003$) and CCL23 (1.50 vs. 0.12; $p = 0.021$) in the CR group. The Human Protein Atlas provided external support for our findings.

Conclusions The results suggest that ARTN and CCL23 may serve as biomarkers for predicting responsiveness to the "7 + 3" induction in untreated AML. Using an enzyme-linked immunosorbent assay to identify the roles of ARTN and CCL23 in predicting AML chemosensitivity may enhance clinical applicability in the future.

Keywords Olink®, Proteomics, Acute myeloid leukemia, Chemosensitivity, ARTN, CCL23

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Backgrounds

Acute myeloid leukemia (AML) is the most common form of leukemia among adults [1]. In the United States, the overall incidence of AML is 4.3 cases per 100,000 individuals, with the rate increasing among older populations [2]. Although the primary mechanism of AML involves the abnormal clonal expansion of immature myeloid blasts because of uncontrolled proliferation and inadequate differentiation of hematopoietic stem cells (HSCs), the precise pathophysiology underlying AML development remains unclear. For untreated patients with de novo AML and an intent to cure, the initial therapy is the "7 + 3" induction chemotherapy, which consists of cytarabine (100 mg/m^2 for 7 days) and idarubicin (12 mg/m^2 for 3 days). This approach can lead to a complete remission (CR) rate of 70%, representing a pivotal phase in the treatment of AML [3]. Following induction therapy, consolidation chemotherapy is essential for patients who achieve a CR. In patients with high-risk cytogenetics or specific genetic mutations, allogeneic hematopoietic stem cell transplantation (allo-HSCT) markedly enhances overall survival (OS) by minimizing the risk of AML recurrence [3].

Patients with AML who fail to reach CR after undergoing the "7 + 3" induction regimen face significantly poor outcomes. Before the introduction of genetic-based risk assessment, predictors of non-responsiveness to the "7 + 3" induction included clinical characteristics such as advanced age, high white blood cell count, and the presence of high-risk cytogenetic features [4]. In recent years, the significance of molecular testing for predicting CR outcomes following induction chemotherapy has steadily increased. A meta-analysis conducted by Daver et al. [5] demonstrated that the CR rate in AML patients with mutated TP53, who were undergoing intensive chemotherapy fell below 50%. Further investigations from one of our prior studies have shown that mitochondrial oxidative phosphorylation, Myc activation, stem cell-like properties, and mTOR signaling are independently linked to chemotherapy resistance in AML [6]. Through single-cell RNA sequencing analysis, we discovered that AML myeloblasts originate from a varied population of HSCs. Furthermore, hematopoiesis cessation occurs earlier in chemotherapy-resistant AML cells [7]. Proteomic analysis, along with genetic testing, may be an additional approach for predicting treatment responses in AML. Among the diverse methods available for proteomic investigation, Olink® offers a specialized platform for conducting plasma proteomic analysis. Although the Olink® platform may not be as flawless as other proteomic platforms for identifying biomarkers in predicting chemosensitivity in AML, the biomarkers identified using the Olink® Explore-384 Inflammation platform could be more easily implemented in clinical settings through the ELISA approach in the future.

As a multiplex proximity extension assay, Olink® proteomic analysis represents a cutting-edge approach in the field of proteomics, leveraging high-throughput technology to quantitatively measure protein levels across a wide array of samples. This technology is renowned for its precision, sensitivity, and scalability, making it an invaluable tool for biomarker discovery, disease research, and the development of personalized medicine strategies [8]. By employing the Olink® Explore platform for plasma proteome analysis, it is possible to identify biomarkers that could potentially pinpoint individuals at the highest risk for lung cancer [9]. The effectiveness of using Olink® to identify biomarkers that predict chemotherapy response to the "7 + 3" induction regimen in AML is still uncertain and requires further exploration.

We hypothesized that AML patients who were chemosensitive differed in plasma protein expression from those who were chemoresistant to the "7 + 3" induction regimen. The current study aimed to employ the Olink® Explore-384 Inflammation platform to compare the plasma proteomic profiles of newly diagnosed *de novo* AML patients who did and did not achieve CR following "7 + 3" induction therapy. Proteins identified by the Olink® Explore-384 Inflammation panel platform would be validated via immunohistochemical (IHC) staining.

Methods

Patients and sample collection

The study prospectively enrolled a total of 43 consecutive de novo AML patients, who underwent "7 + 3" or "7 + 3"-like induction therapy from March 2020 to June 2021 at Taichung Veterans General Hospital. These patients were categorized into the following two groups based on their bone marrow status, assessed approximately 28 days post-induction chemotherapy: the CR group ($n = 29$) and non-CR group ($n = 14$) (Table 1). Bone marrow samples were collected from the patients at the time of diagnosis. Plasma was isolated from the samples using EDTA tubes and centrifuged at 400 × g for 15 min at room temperature. The resultant plasma was then transferred to fresh tubes and stored at -80 °C for future analysis.

This study was approved by the Institutional Review Board of the Taichung Veterans General Hospital following the latest version of the Declaration of Helsinki (CF17319B). All the participants provided informed consent before participating in the study. The patient details were anonymized.

Table 1 Patient characteristics

	All patients (*n* = 43)	Non-CR group (*n* = 14)	CR group (*n* = 29)	*p*
Age, y (mean ± SD)	51.1 ± 11.7	51.8 ± 13.4	50.7 ± 11.0	0.784[a]
Sex (n, %)				
Male	24 (55.8)	9 (64.3)	15 (51.7)	0.523[c]
Female	19 (44.2)	5 (35.7)	14 (48.3)	
Leukocytes, 10^3/μL (mean ± SD)	63.4 ± 71.4	46.5 ± 55.2	71.0 ± 77.2	0.235[a]
Blasts in marrow, % (mean ± SD)	54.3 ± 21.7	60.7 ± 20.1	51.3 ± 22.2	0.184[a]
Blasts in PB, % (mean ± SD)	32.3 ± 28.3	33.7 ± 25.3	31.6 ± 30.1	0.821[a]
FAB classification (n, %)				
M0	2 (4.7)	1 (7.1)	1 (3.4)	0.585[b]
M1	2 (4.7)	1 (7.1)	1 (3.4)	
M2	23 (53.5)	8 (57.2)	15 (51.8)	
M4	10 (23.2)	2 (14.4)	8 (27.6)	
M5	5 (11.6)	1 (7.1)	4 (13.8)	
M6	1 (2.3)	1 (7.1)	0 (0.0)	
Cytogenetics (n, %)				
Favorable	5 (11.6)	0 (0.0)	5 (17.2)	0.098[b]
Intermediate	19 (44.2)	5 (35.7)	14 (48.3)	
Unfavorable	19 (44.2)	9 (64.3)	10 (34.5)	
Molecular mutation (n, %)				
FLT3 ITD mutation	6 (14.0)	1 (7.1)	5 (17.2)	0.645[c]
NPM1 mutation	9 (20.9)	0 (0.0)	9 (31.0)	0.020[c]

CR: complete remission; SD: standard deviation; PB: peripheral blood; FAB: French-America-British

Data were compared using Independent [a] Sample t test, [b] chi-square test, [c] Fisher's exact test

Characterization of inflammation-related proteins with Olink® explore 384-Panel

The Olink® Explore 384-panel inflammation panel (Olink® Proteomics, Uppsala, Sweden) was used to measure protein levels in the bone marrow plasma derived from patients with de novo AML according to the manufacturer's instructions. The unit of measurement was normalized protein expression (NPX), a proprietary scale unique to Olink® that uses a Log2 scale. NPX values, which reflect protein expression levels, were calculated through a normalization process involving counts from next-generation sequencing (NGS). Higher NPX values indicate higher protein concentrations. The differential expression of proteins (DEPs) between groups was analyzed using the "OlinkAnalyze" R package. Volcano plots and heatmaps were created using ggplot2 to illustrate protein expression patterns. Gene Ontology (GO) terms were used to identify gene sets using the enriched R package.

Immunohistochemical (IHC) validation

We validated the results of the Olink® proteomic analysis using IHC staining on bone marrow biopsy specimens. IHC staining for ARTN, CCL23, and CCL13 was performed according to established protocols. Tissue sections were deparaffinized and rehydrated, followed by antigen retrieval. We blocked endogenous peroxidase activity and prevented nonspecific binding with suitable blocking solutions. Sections were incubated with primary antibodies against ARTN (AF258, R&D Systems, Minneapolis, USA), CCL23 (ab24593, Abcam, Cambridge, UK), and CCL13 (ab171751, Abcam, Cambridge, UK) at optimized dilutions. After washing, the sections were incubated with horseradish peroxidase-conjugated secondary antibodies. Protein expression was visualized using a diaminobenzidine substrate and the sections were dehydrated subsequently, mounted, and examined under a microscope.

After preparing the IHC stains for ARTN, CCL23, and CCL13 expression, a hematopathologist quantified the staining. The assessment involved scoring the average percentage of antibody-stained tumor cells across three fields at 400× magnification. Staining intensity was graded on a scale from negative (0), indicating no staining, to strongly positive (3+), indicating strong and distinct cytoplasmic staining. Weakly positive (1+) was defined as faint but perceptible staining, whereas moderately positive (2+) represented the intensity between weak and strong positive staining (Supplemental Fig. 1) [10].

Statistical analysis

To compare clinical characteristics, categorical variables were analyzed using either the chi-squared test or Fisher's exact test, as appropriate, while continuous variables were assessed using Student's t-test. Statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). Besides, the Olink® proteomic analysis was performed using the "Olink®Analyze" software package (Version 3.2.2, city, country) in R. Statistical significance was established at $P < 0.05$.

Results

Patient characteristics comparison

A demographic comparison between the CR ($n = 29$) and non-CR ($n = 14$) groups are presented in Table 1. The average ages were 50.7 ± 11.0 and 51.8 ± 13.4 years, respectively, with no significant difference ($p = 0.784$). Similarly, there were no significant differences between the groups in terms of sex ($p = 0.523$), leukocyte counts at diagnosis ($p = 0.235$), myeloblasts in the bone marrow ($p = 0.184$) and peripheral blood ($p = 0.821$), French-American-British classification ($p = 0.585$), or cytogenetic risk ($p = 0.098$). The proportions of the FLT3 ITD mutation were also comparable ($p = 0.645$). However, the incidence of the NPM1 mutation was significantly higher

in the CR group at 31.0%, than 0% in the non-CR group ($p = 0.020$).

Differential protein expression identified by the proteomic analysis

Proteomic analysis was performed using the Olink® inflammatory platform, enabling a comprehensive evaluation of bone marrow plasma protein expression profiles in both CR and non-CR patients (Supplemental Fig. 2). To identify the differentially expressed proteins between these two groups, a heat map was used to display the top 10 proteins with the most significant differences, ranked by p-value (Fig. 1A). The results showed that LTBR, ARTN, BCL2L11, LGMN, CRHBP, OSM, CCL23, and IL18R1 were highly expressed in the CR group, whereas CCL13 and IL2 were highly expressed in the non-CR group. A volcano plot was used to further visualize the differences in protein expression, showing proteins with a p-value < 0.05 and absolute Log2FC greater than 1 (Fig. 1B). This dual criterion approach ensures not only statistical significance but also meaningful differences in expression, making it possible to select biomarkers with more pronounced variations. Notably, ARTN expression levels were 2.9 ± 0.46 NPX in the CR group and 0.9 ± 0.42 NPX in the non-CR group, showing significantly higher levels in CR patients compared to non-CR patients ($p = 0.009$) (Fig. 2A). Similarly, CCL23 expression levels were 2.6 ± 0.23 NPX in the CR group and 1.5 ± 0.24 NPX in the non-CR group, also significantly elevated in CR patients ($p < 0.001$) (Fig. 2B). In contrast,

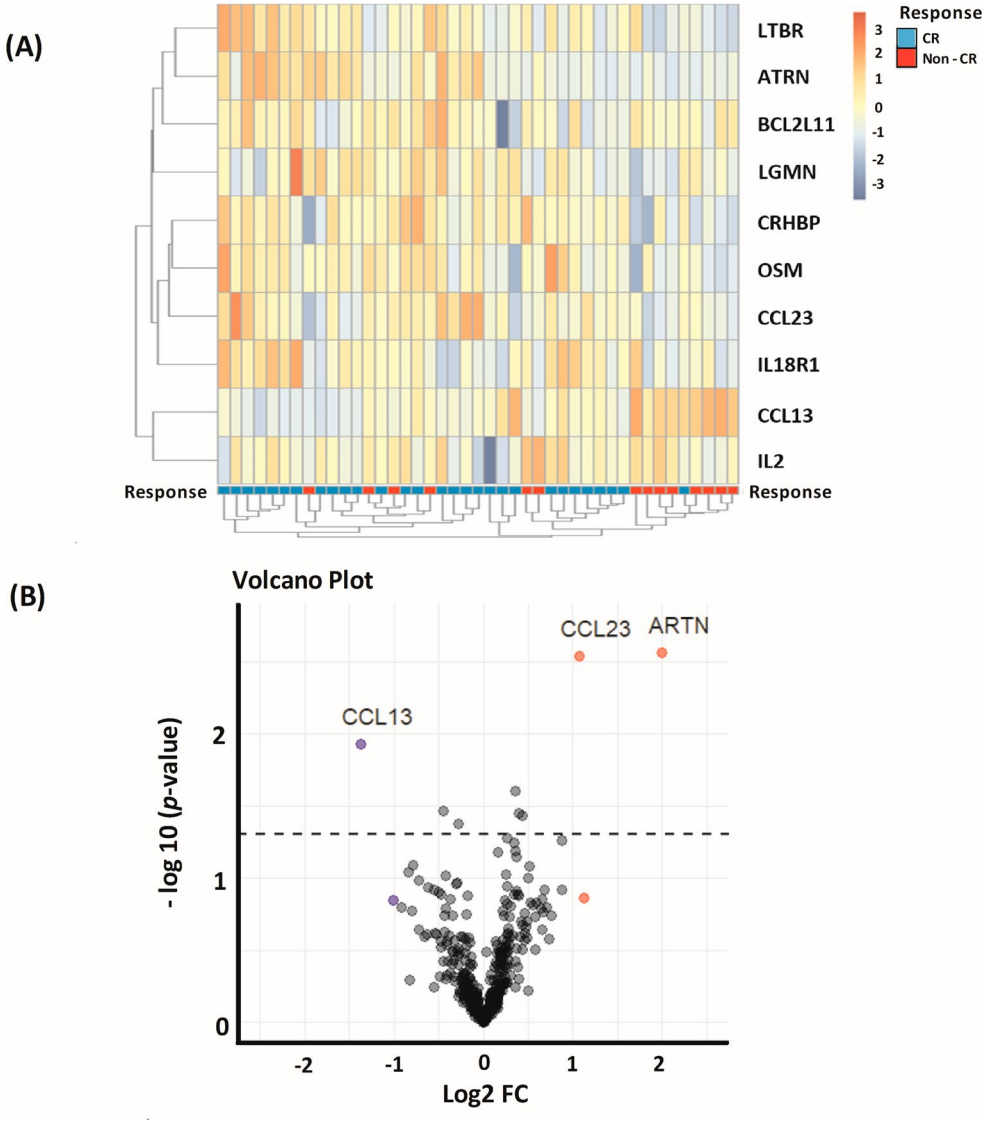

Fig. 1 Differentially expressed inflammation-related biomarkers between AML patients in CR or non-CR. (**A**) Heatmap of top 10 differentially expressed proteins. Volcanic visualization of 384 inflammation-related biomarkers. (**B**) Volcanic visualization of 384 inflammation-related biomarkers. The dashed line represents a p-value < 0.05. Blue spots indicate a log2 fold change (FC) of less than − 1, while red spots represent a log2 FC of greater than 1

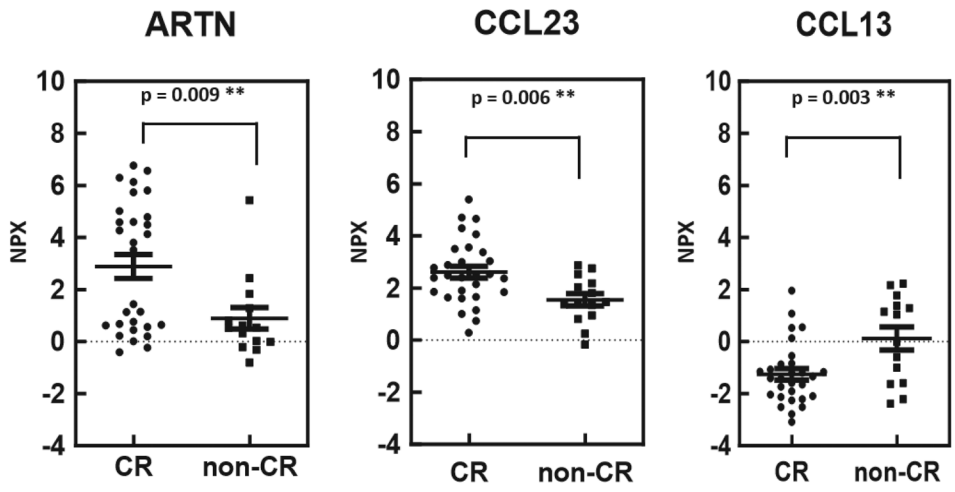

Fig. 2 Protein expressions between complete remission (CR) and non-CR. The scatter plot displays individual data points for the CR and non-CR groups. Normalized protein expression (NPX) represents protein expression levels, illustrating the distribution and central tendency of a quantified variable. The central horizontal line marks the mean value, whereas the error bars represent the standard error of the mean (SEM), providing insights into the variability and skewness within each group. The dotted lines indicate that NPX = 0. *$P < 0.05$, **$P < 0.01$

CCL13 expression was notably lower in CR patients (CR group: -1.3 ± 0.22 NPX vs. non-CR group: 0.12 ± 0.44 NPX; $p = 0.003$) (Fig. 2C). These observations suggest that ARTN, CCL23, and CCL13 may be potential biomarkers linked to the response to "7 + 3" induction therapy.

Validation of proteomic analysis via immunohistochemical staining and mRNA expression

To confirm that the plasma levels of ARTN and CCL23 were higher and that CCL13 was lower in CR patients, we used IHC staining of bone marrow tissues to validate these findings. The results indicate that the expression levels of ARTN and CCL23 were higher in CR patients than in the non-CR patients. However, the expression of CCL13 was similar between the two groups (Fig. 3A). To quantify the expression of ARTN, CCL23, and CCL13 by IHC staining, we calculated the average percentage of antibody-stained tumor cells across three different fields at 400× magnification and assigned scores of 0, 1+, 2+, and 3 + to their expression levels. The results indicated that CR patients had more 3 + expression of ARTN (25.40% vs. 7.05%; $p = 0.013$) and CCL23 (24.14% vs. 14.29%; $p = 0.039$) than did non-CR patients, which was consistent with the plasma proteomic analysis. However, the 3 + expression levels of CCL13 were similar between CR and non-CR patients (63.44% vs. 57.58%; $p = 0.289$), which did not support the findings of the plasma proteomic analysis (Fig. 3B). This discrepancy could be partially attributed to the nature of the Olink® platform, which primarily identifies secretory proteins, while IHC staining detects cytoplasmic and membranous proteins that may not be fully secreted into the plasma.

We used the bulk RNA-seq dataset (GSE164894) to corroborate the plasma proteomic analysis data. Our findings revealed that ARTN mRNA expression levels were 1.93 in the CR group and − 0.09 in the non-CR group ($p = 0.003$). Similarly, the CCL23 mRNA expression was 1.50 in the CR group and 0.12 in the non-CR group ($p = 0.021$) (Fig. 3C). These results further confirmed that the expressions of both ARTN and CCL23 were higher at the mRNA level in patients with CR than in those without. We also utilized the Human Protein Atlas [11] for external validation, demonstrating that ARTN (median: 0.983 NPX, $n = 48$) and CCL23 (median: 2.455 NPX, $n = 48$) were expressed at significantly higher levels ($p < 0.001$) in AML patients compared to those with other cancers (Fig. 3D and supplementary Table 1). Given that AML is more sensitive to chemotherapy than other cancers, this finding partially supported the potential relevance of ARTN and CCL23 as chemosensitivity biomarkers in AML.

Potential biological pathways of ARTN and CCL23 for chemosensitivity in AML

To explore how ARTN and CCL23 influence chemosensitivity in AML, we performed a pathway analysis using GO enrichment. While no pathways met the adjusted p-value threshold (< 0.05) after multiple testing correction, we adopted an exploratory approach by analyzing differentially expressed proteins with a nominal p-value < 0.05 and Log2FC > 1 to identify potential pathways associated with chemosensitivity. The top five pathways identified are shown in Fig. 4. The analysis revealed that the genes encoding ARTN and CCL23 participate in a variety of biological processes. Specifically, ARTN is

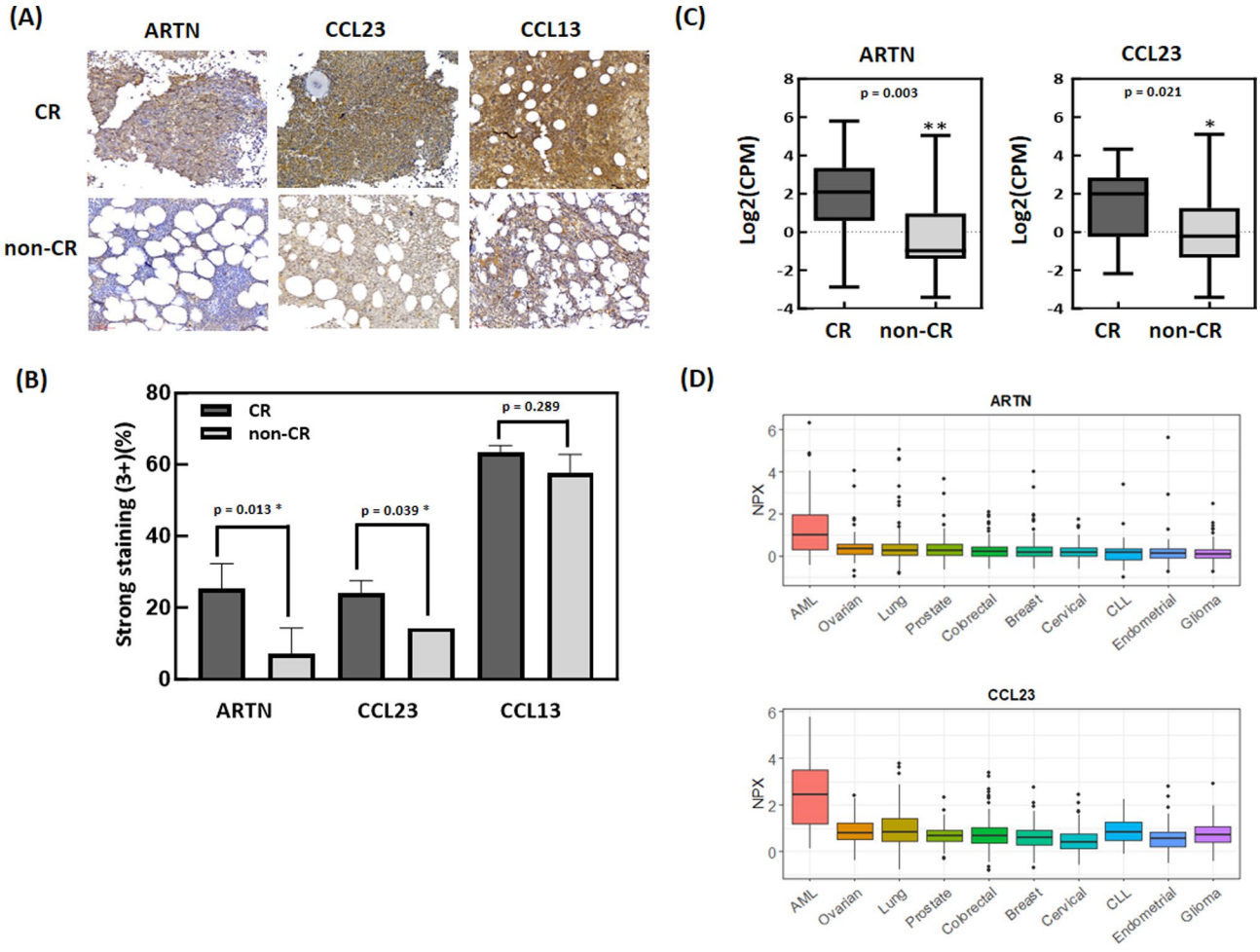

Fig. 3 Immunohistochemical (IHC) staining and mRNA expression of candidate expression in acute myeloid leukemia (AML) patient specimens. (**A**) Representative images of IHC staining for ATRN, CCL23, and CCL13 (×400), showing sections from patients with complete remission (CR) at the top and non-CR at the bottom. (**B**) The bar graph illustrates the percentage of patients showing strong staining intensity (3+) for each antibody. It compares the proportions of CR and non-CR group patients with strong staining. A t-test determined the statistical significance of differences in staining intensity between the CR and non-CR groups, indicated by * $p < 0.05$. (**C**) The Log2 (CPM) expression levels of ARTN and CCL23 from bulk RNA-seq analysis comparing CR and non-CR groups in acute myeloid leukemia patients are shown. The box plot represents the 25th and 75th percentiles, with whiskers indicating the maximum and minimum values. Solid lines within the boxes mark the medians. Statistical significance is denoted by * $p < 0.05$ and ** $p < 0.01$. (**D**) The Human Protein Atlas data show that ARTN and CCL23 are expressed at significantly higher levels ($p < 0.001$) in AML patients compared to those with other cancers

closely linked to neuroblast proliferation and the development of the peripheral nervous system. Conversely, CCL23 was strongly associated with immune-related functions such as lymphocyte migration, monocyte chemotaxis, and lymphocyte chemotaxis (Fig. 4). This study underscores the distinct roles of ARTN and CCL23 in AML chemosensitivity, showing that, while ARTN is pivotal for the development of the nervous system, CCL23 is crucial for the immune system dynamics.

Predictive power of ARTN and CCL23

After these observations, we evaluated the predictive capability of 3 + ARTN and CCL23 expression levels in determining the response to the "7 + 3" chemotherapy regimen in AML patients, as shown in Table 2. Our results indicated that patients with 3 + ARTN expression achieved a CR rate of 100.00%. The sensitivity and specificity were 20.69% and 100.00%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were measured at 100.00% and 37.84%, respectively. Similarly, 3 + CCL23 resulted in a CR rate of 81.82%, with a sensitivity of 31.03% and a specificity of 85.71%. The PPV and NPV for CCL23 expression were 81.82% and 37.50%, respectively. When both ARTN and CCL23 were strongly positive (3+), the CR rate reached 100%, with a PPV and NPV of 100.00% and 36.84%, respectively. These findings indicate that IHC-based expression profiling of ARTN and CCL23 could potentially serve as biomarkers for predicting the chemosensitivity to the "7 + 3" induction therapy in AML patients.

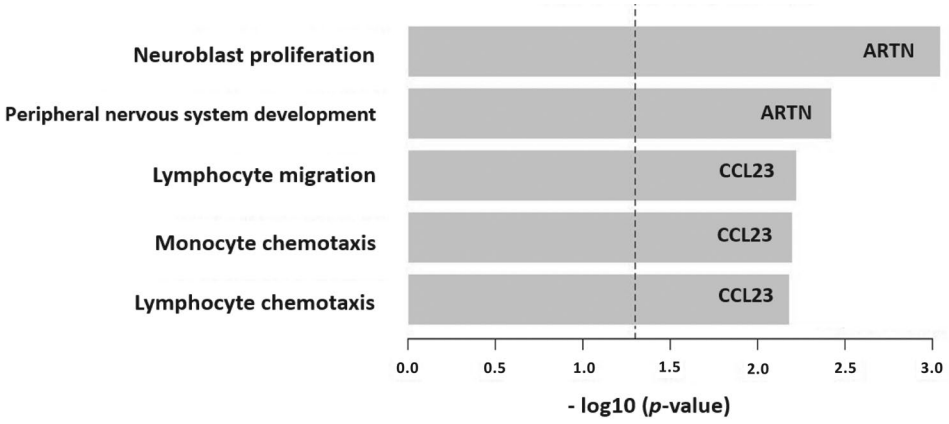

Fig. 4 Biological processes identified in gene ontology analysis. Gene ontology analysis reveals the biological processes most significantly enriched among differentially expressed proteins. The bar graph highlights the top five pathways

Table 2 "7 + 3" induction response prediction by high ARTN and CCL23 expressions

		Total (*n*)	Non-CR (*n*)	CR (*n*)	Sensitivity	Specificity	PPV	NPV	Accuracy
ARTN (3+)	Yes	6	0	6	20.69%	100.00%	100.00%	37.84%	46.51%
	No	37	14	23					
CCL23 (3+)	Yes	11	2	9	31.03%	85.71%	81.82%	37.50%	48.84%
	No	32	12	20					
ARTN (3+) & CCL23 (3+)	Yes	5	0	5	17.24%	100.00%	100.00%	36.84%	44.19%
	No	38	14	24					

CR: complete remission; PPV: positive predictive value; NPV: negative predictive value

Discussion

The current study used the Olink® inflammation platform for proteomic analysis to investigate differences in bone marrow plasma protein levels between de novo AML patients undergoing the "7 + 3" induction with and without CR achievements. The results indicated that patients with CR exhibited higher expression levels of ARTN and CCL23 proteins than did those without CR. This finding was further validated via IHC staining of bone marrow specimens and RNA-Seq databases. These data suggest that ARTN and CCL23 in the bone marrow plasma could serve as potential biomarkers for predicting chemosensitivity in AML.

The use of proteomics for AML is increasing. Through proteomic analysis, researchers have distinguished five AML subtypes, two of which are significantly correlated with patient outcomes [12]. Recently, a multiplex proximity extension assay conducted on diagnostic plasma specimens revealed that acute leukemia samples contain elevated levels of proteins linked to inflammation, hemostasis, cell differentiation, and cell-matrix integration [13]. Rossi et al. [14] demonstrated that, in patients with advanced melanoma, circulating inflammatory proteins correlated with their response to immune checkpoint inhibition therapy. Our study demonstrated that higher levels of ARTN and CCL23 in the bone marrow plasma, measured using a multiplex proximity extension assay, could predict chemosensitivity in AML patients undergoing "7 + 3" induction therapy. We further applied these findings clinically and observed that the CR rates for patients exhibiting strong ARTN and CCL23 expression, as determined via IHC staining, were 100% and 81.82%, respectively.

The association between ARTN and chemosensitivity in AML remains unclear. However, interactions between ARTN and cancers other than AML have also been documented. ARTN is known to promote the progression of human carcinomas while enhancing the migration and invasion abilities of cancer cells [15, 16]. Moreover, studies have shown a positive correlation between high ARTN expression and increased responsiveness to radiotherapy in nasal and other cancers [17]. As a ligand of the glial cell line-derived neurotrophic factor family, ARTN plays a crucial role in the bone marrow microenvironment by affecting various physiological and pathophysiological processes. By interacting with the GFRα3 receptor, ARTN activates and sensitizes nerve growth factor-sensitive bone afferent neurons. This signaling pathway is the key to the development of inflammatory bone pain, emphasizing the pivotal role of ARTN-mediated mechanisms in this pain phenotype [18]. Furthermore, the presence of GFRα3 in non-neuronal bone marrow cells, particularly those near blood vessels and nerve fibers, suggests a broader physiological role for ARTN in this environment.

This underscores the impact of ARTN on bone marrow neuroimmunological dynamics [19]. Although the detailed mechanism remains unclear, ARTN-associated chemosensitivity in AML may arise from alterations in the bone marrow microenvironment.

In terms of the potential role of CCL23 on AML chemosensitivity, CCL23 plays a pivotal role in the chemotaxis of monocytes and lymphocytes. A study by Shih et al. [20] demonstrated that CCL23 regulates myeloid cell dynamics in AML. Another study monitoring minimal residual disease in AML revealed that CCL23 is significantly overexpressed in leukemia cells compared to other hematopoietic cells in the bone marrow, and this overexpression decreases significantly when patients achieve CR [21]. Furthermore, the upregulation of CCL23 and its association with changes in protein signaling networks may enhance leukemia cell survival and influence the efficacy of chemotherapy [22]. These findings corroborate our proteomic analysis data, suggesting that CCL23 could be a vital biomarker for predicting complete remission in patients with AML undergoing induction chemotherapy. Taken together, CCL23 not only plays a critical role in the dynamics of bone marrow cells in AML but also holds significant potential for improving disease monitoring and therapeutic strategies.

The primary limitation of this study was its small sample size. In addition, validation using independent cohorts is required to confirm our results. We have thoroughly investigated AML-related proteomics studies and databases, including the Proteomic Data Commons [23–25]. Additionally, we analyzed the Reverse Phase Protein Array data from TCGA. Despite our efforts, we did not observe significant differential expression of ARTN and CCL23 in these datasets. The lack of consistent findings could be attributed to variations in sample processing methods across the datasets. Nevertheless, we found evidence in the Human Protein Atlas [11] suggesting that ARTN and CCL23 were expressed at higher levels in AML patients compared to other cancers. Given that AML is more sensitive to chemotherapy than other cancers, this finding underscores the potential relevance of ARTN and CCL23 as chemosensitivity biomarkers in AML.

In conclusion, our study emphasizes the significant roles of ARTN and CCL23 in the bone marrow plasma as biomarkers for predicting chemosensitivity in patients with AML undergoing "7 + 3" induction chemotherapy. IHC staining and RNA sequencing confirmed our findings at the protein and gene levels, respectively. The predictive capabilities of ARTN and CCL23 underscore their value for customizing AML treatment strategies. Further research is needed to elucidate the mechanistic pathways and develop targeted therapies to improve the therapeutic efficacy and patient outcomes in AML. Using an enzyme-linked immunosorbent assay to identify the roles of ARTN and CCL23 in predicting AML chemosensitivity may enhance clinical applicability.

Abbreviations

AML	acute myeloid leukemia
HSCs	hematopoietic stem cells
CR	complete remission
Allo-HSCT	allogeneic hematopoietic stem cell transplantation
OS	overall survival
IHC	immunohistochemical
NPX	normalized protein expression
DEP	differential expression of protein
GO	Gene Ontology
PPV	positive predictive value
NPV	negative predictive value

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

TW: Conceptualization, Investigation, Formal analysis, Writing – review & editing. TH: Conceptualization, Methodology, Investigation, Writing – review & editing. CC: Methodology, Investigation, Writing – review & editing. HL: Methodology, Investigation, Writing – review & editing. MH: Methodology, Investigation, Writing – review & editing. PJ: Methodology, Investigation, Writing – review & editing. JT: Methodology, Investigation, Writing – review & editing. CJT: Conceptualization, Supervision, Writing – review & editing. All authors gave final approval of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Taichung Veterans General Hospital following the latest version of the Declaration of Helsinki (CF17319B). All the participants provided informed consent before participating in the study. The patient details were anonymized.

Consent for publication

We confirm that the material is original research, has not been published elsewhere in part or in entirety and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to *Clinical Proteomics*.

Competing interests
Chieh-Lin Jerry Teng received honorarium and consulting fees from Novartis, Roche, Pfizer, Takeda, Johnson and Johnson, Amgen, BMS Celgene, Kirin, and MSD. The other authors have no conflicts of interest.

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