RESEARCH PAPER

The LncRNA ZNF674-AS1 / miR-181a / SOCS4 / STAT3 Axis as a Novel Molecular Target and Diagnostic Biomarker in Pancreatic Cancer

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ABSTRACT

Background: Pancreatic carcinoma (PC) is one of the most prevalent and deadliest gastrointestinal cancers in humans. PC is often driven by chronic inflammation, resulting in genetic dysregulation. Identifying non-invasive biomarkers contributing to PC molecular pathogenesis is mandatory for early detection, hence better patient outcomes. **Methods:** Expression profiles of the lncRNA ZNF674-AS1/miR-181a/SOCS4/STAT3 regulatory axis were investigated in the serum of 110 participants, including 55 patients with pancreatic cancer (PC) and 55 healthy controls. Serum expression levels of lncRNA ZNF674-AS1, miR-181a, and STAT3 were quantified using quantitative real-time PCR (qRT-PCR), while serum SOCS4 protein concentrations were measured by enzyme-linked immunosorbent assay (ELISA). The diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. **Results:** Serum lncRNA ZNF674-AS1 expression and SOCS4 protein levels were significantly lower in patients with PC than in healthy controls, whereas miR-181a and STAT3 expression levels were significantly higher ($P < 0.05$). ROC curve analysis demonstrated that lncRNA ZNF674-AS1 (AUC = 0.99) and STAT3 (AUC = 0.96) may serve as diagnostic biomarkers for PC, with lncRNA ZNF674-AS1 achieving a sensitivity of 98.2% and a specificity of 100% at a cut-off value of ≤ 0.62. **Conclusions:** Our findings demonstrate a novel dysregulation in the expression pattern of the lncRNA ZNF674-AS1/miR-181a/SOCS4/STAT3 regulatory axis in pancreatic cancer (PC). We propose that reduced lncRNA ZNF674-AS1 expression is associated with PC progression through miR-181a upregulation, SOCS4 suppression, and STAT3 hyperactivation. This proposed serum-based regulatory mechanism may provide a highly sensitive and specific biomarker signature for the non-invasive diagnosis and clinical management of pancreatic adenocarcinoma.

Keywords: PC; lncRNA ZNF674-AS1; miR-181a; SOCS4; STAT3

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INTRODUCTION

Pancreatic carcinoma is one of the deadliest forms of cancer, with one of the highest mortality rates, largely due to its late diagnosis and aggressive disease progression. The etiology of pancreatic carcinoma is linked to genetic alterations that interact through complex and interconnected molecular mechanisms [1]. Early identification of PC remains difficult due to the lack of sufficiently sensitive and specific biomarkers, despite the critical need for earlier detection to reduce its high mortality rate. The most widely used biomarker, CA 19-9, lacks adequate sensitivity and specificity for early-stage detection, as its levels are typically elevated only in advanced disease, thereby limiting its clinical utility for early diagnosis [2]. Chronic inflammation, genetic predisposition, and behavioral risk factors strongly influence the risk of developing PC [3]. These risk factors can be classified into: (i) modifiable factors, such as obesity and (ii) non-modifiable factors, including inherited genetic factors, which account for approximately 10% of PC cases [4].

Non-coding RNAs (ncRNAs) are RNA molecules that are non-protein-coding but have remarkable regulatory functions on gene expression. They are divided into two classes: housekeeping ncRNAs and regulatory ncRNAs. Regulatory ncRNAs are subclassified as microRNAs (miRNAs), small interfering RNAs, piwi-interacting RNAs, long non-coding RNAs (lncRNAs), and circular RNAs [5]. ncRNAs have garnered significant interest owing to their pivotal roles in tumor initiation and progression, particularly in mediating resistance to immunotherapy [6]. Long non-coding RNA zinc finger protein 674 antisense RNA 1 (lncRNA ZNF674-AS1) a single stranded RNA consisting of 2,148 nucleotides cited

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on chromosome band Xp11.3. It was first identified through lncRNA expression profiling in hepatocellular carcinoma (HCC) expression profile of lncRNAs [7,8]. MicroRNA-181a (miR-181a) is a highly conserved member of the miR-181 family [9]. Aberrant upregulation of miR-181a has been reported in several malignancies, including colorectal, gastric, breast and thyroid cancers. Inhibition of miR-181a significantly suppresses thyroid cancer cell proliferation while promoting apoptosis, highlighting its potential oncogenic role [10,11].

Suppressors of cytokine signaling family member 4 (SOCS4) have been demonstrated to play a crucial role in progression of numerous malignancies, including HCC, lung adenocarcinoma, breast cancer, and thyroid cancer [12]. Lower levels of SOCS protein have been frequently reported in cancers, accompanied by persistent activation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling axes, tumor aggressiveness, and poor prognosis [13]. Signal transducer and activator of transcription 3 (STAT3), a member of the STAT protein family is phosphorylated by kinases, resulting in heterodimers that migrate to the nucleus where they play role as transcription factors crucial in numerous cellular functions, as in cell growth and apoptosis [14].

Correlation among lncRNA ZNF674-AS1, miR-181a and SOCS4 has been investigated in thyroid cancer (TC) where lncRNA ZNF674-AS1 suppressed thyroid cancer progression by regulating the miR-181a/SOCS4 axis. Overexpression of lncRNA ZNF674-AS1 hindered cancer cells migration, proliferation and invasion in vitro and suppressed tumor growth in vivo, suggesting that lncRNA ZNF674-AS1 functions as a molecular sponge for miR-181a thus increasing SOCS4 expression [10]. Inhibition of SOCS4 has been shown to promote cancer proliferation and invasion in human kidney, via augmented (JAK-STAT) pathway [15]. In this study, we aimed to elucidate the lncRNA ZNF674-AS1/miR-181a/SOCS4/STAT3 regulatory axis in the serum of pancreatic adenocarcinoma patients, correlating their expression levels to their histopathological gradings as well as evaluate their potential utility of these markers as clinical biomarkers.

SUBJECTS AND METHODS

Ethical approval and samples collection

The total sample size calculated was 110 subjects: (55 pc patient and 55 healthy control), the required sample size was computed based on a power analysis (G*Power 3.1.9.2; Faul, Erdfelder, Lang, & Buchner, 2007). With alpha = .05 and power = .80, the projected sample size needed to detect a medium effect size (d = .50) for a t test difference from a constant is at least n = 51 for each group. Subjects were recruited from Internal Medicine department, Kasr Alainy, Cairo University Hospitals after obtaining study ethical approval by ethical committee of Kasr Alainy hospitals: code (MD-134-2024). All participants signed informed consents. Subjects were divided into; group I with 55 PC patients, based on histopathological evaluation following endoscopic ultrasound-guided fine needle biopsy (Pentax EG-3870UTK/Hitachi Avius, Tokyo, Japan) and group II of 55 healthy subjects with no history of pancreatic diseases as a Control group. All assessment methods were carried out at Medical Biochemistry and Molecular Biology department, Faculty of Medicine, Cairo University.

Quantitation of Human SOCS4 by ELISA

Human serum SOCS4 concentrations were measured using a commercial ELISA kit (SUNLONG BIOTECH Co., Ltd., China) based on the Sandwich- immunoassay method, Briefly, standardized volumes of serum samples and standards were added to microplate wells pre-coated with a SOCS4-specific antibody, allowing SOCS4 to bind to the immobilized antibody. A Horseradish Peroxidase conjugated to the antibody specific to SOCS4 was then added into to the microplate wells. After the required incubation and washing steps, a chromogenic substrate was added to each well rendering samples coloration proportionate to SOCS4 concentration, The optical density (OD) was measured using a spectrophotometer. The OD or absorbance of standards was plotted against the calibrators concentrations to generate a calibration curve, from which the serum SOCS4 concentrations in patient samples was calculated by interpolation using Graphpad prism10.

Molecular techniques

RNA extraction:

Total RNA with preserved non coding RNAs was extracted from serum samples by miRNeasy extraction kit (Qiagen, Germany). Briefly, serum samples were lysed using QIAzol Lysis Reagent, The RNA-containing aqueous phase was subsequently combined with absolute ethanol and placed into a spin column, followed by multiple washing and centrifugation procedures. finally, elution was done to collect the extracted RNA. RNA concentration in each sample was assayed by Nanodrop using (Quawell UV-Vis spectrophotometer Q5000 California, USA).

Reverse transcription (RT) and Quantitative Real-time PCR (qPCR) for miRNA-181a

RT and qPCR were performed by Rotor-Gene Q Real-Time PCR system (Qiagen, USA). Isolated RNA was reverse transcribed then amplified using miRCURY LNA miRNA PCR starter Kit (Qiagen,Maryland, USA). Complementary DNA (cDNA) was synthesized from isolated RNA template in a mix of final volume of 10 µL with reverse transcriptase enzyme mix and RNAase free water. The mixture was incubated at 42 °C for 60 minutes, reverse transcriptase was subsequently inactivated by heating at 95 °C for 5 minutes, followed by qPCR amplification of cDNA, each 10 µL PCR reaction contained SYBR Green PCR master mix, the cDNA template, RNase-free water, and miR-181a specific primers (Qiagen GeneGlobe ID YP002006081). miR-181a was normalized to the endogenous reference gene U6 (Qiagen GeneGlobe ID YP02119464). The thermocycling parameters included an initial activation at 95°C for 2 minutes, succeeded by 40 cycles of denaturation at 95°C for 10 seconds and simultaneous annealing, extension, and fluorescence data collection at 56°C for 60 seconds.

RT and qPCR for for lncRNA ZNF674-AS1, and STAT3.

A 60ug of extracted RNA was reverse transcribed using cDNA synthesis kit by (TransGen Biotech, China) in a total volume of 20 µL containing reverse transcriptase enzyme, deoxy-nucleotide triphosphates (dNTPs) and RNAase free water, cDNA expression was subsequently amplified and quantified using (TransGen Biotech, China) Syber Green

qPCR kit, Each PCR reaction was performed in a final volume of 20 µL containing SYBR Green PCR master mix, the cDNA template, RNase-free water and gene specific primers ZNF674-AS1 F: 5'GCGTCCTAAGAGCAACAGGT3' and R: 5'TCCCAGACCCAGACAGGAAA3' (NCBI accession number: NR_015378.3), STAT3 primers F: 5'GAGAAACAGTTGGGACCCCT3' R: 5'GCATCTTCTGCCTGGTCACT3' (NCBI accession number: NM_001384993) with GAPDH as housekeeping gene F: 5'TCCAAAATCAAGTGGGGCGA3' R: 5' AAATGAGCCCCAGCCTTCTC3' (NCBI accession number: NM_002046.7). The thermal cycler was programmed with enzyme activation step at 94 °C for 30 seconds, followed by 40 cycles of denaturation at 94 °C for 5 seconds, annealing/Extension and data collection at 60 °C for 30 seconds. Cycle threshold (Ct) values for lncRNA ZNF 674-AS1, miR-181a, STAT3 and the housekeeping (reference) genes were collected. All target genes expression was assayed by the ΔΔCT method, target markers fold change gene expression was calculated by the $2 - (\Delta\Delta CT)$ equation.

Data and Statistical Analysis

Statistical Package of Social Science (SPSS) software version 22.0 on Windows 8.1 (SPSS Inc., Chicago, IL, USA) was used. Kruskal-Wallis test was used to detect normality. For quantitative parametric data Independent Student t-test, mean average and standard deviation (SD) were used. While for qualitative non-parametric data, Chi-square test ($\chi 2$), frequencies, percentages, median and Interquartile Range (IQR) were used. Quantitative variables correlations, Pearson correlation (r) and Spearman's rho correlation coefficient test was performed for parametric non-parametric data respectively. ROC curves were carried out at a significance of ≤ 0.05

RESULTS

Demographic and histopathological grading

The study cohort comprised 110 participants, including 55 patients with PC and 55 healthy controls. Within the PC group, 56.4% were male. Histopathological analysis revealed that 76.4% of cases were grade II, while 23.6% were grade III. According to TNM staging, the PC cohort was distributed as follows: stage II (18.2%), stage III (69.1%), and stage IV (12.7%).

LncRNA ZNF674-AS1, miR-181a, STAT3 expression and SOCS4 levels in serum

In the serum patients with PC, lncRNA ZNF674-AS1 expression was significantly downregulated (0.105-fold; P <0.05), whereas miR-181a expression was markedly upregulated by (2.39-fold; P <0.05) (Fig.1a and 1b) respectively. Similarly, STAT3 gene expression levels were significantly elevated by (4.65-fold; P <0.05) in the PC cohort compared to healthy controls. Furthermore, Serum concentrations of SOCS4 were significantly lower in PC patients (131.33 ±34.39) than in healthy subjects (180.41 ±25.85; P <0.05) (Figure 1c and 1d) respectively.

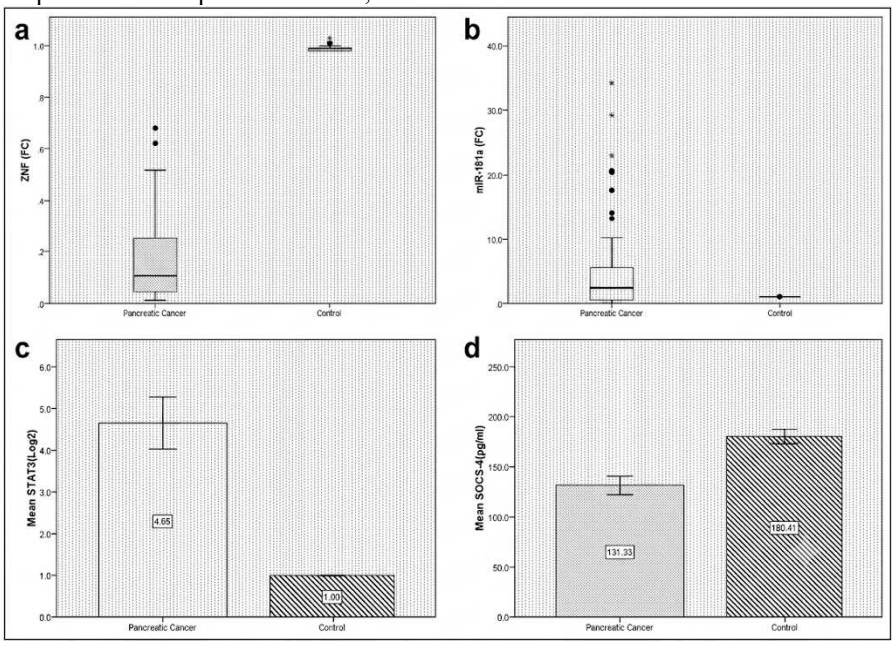


Figure 1: Box Plot demonstrates the expression levels in fold change of (a) lncRNA ZNF674-AS1; downregulated, (b) miR-181a; upregulated (c) STAT3; upregulated and (d) decreased SOCS4 protein level in serum of PC group versus healthy control group.

Regarding histopathological grading, miR-181a showed notable increase in relative gene expression in pancreatic adenocarcinoma grade III (3.41-fold) compared to adenocarcinoma grade II (1.23-fold P <0.05) (Figure 2a). Similarly, following TNM staging only miR-181a showed a statistically significant increase in its expression between Stage III (2.65- fold) and Stage II (1.02-fold P value=0.05) (Figure 2b) while no notable changes in lncRNA ZNF674-AS1 were observed, STAT3 expression or SOCS4 levels between different histopathological gradings or TNM staging in serum of PC patients.

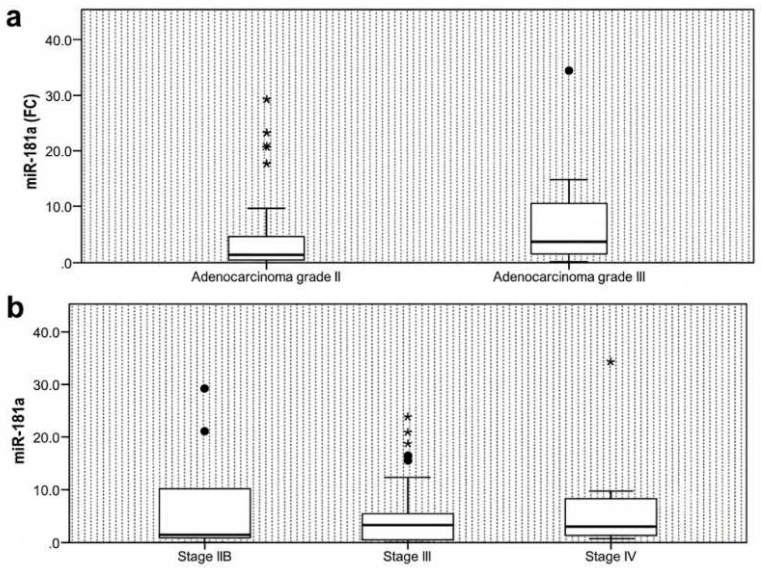


Figure 2: Box plot diagram (a) significant upregulation of miR-181a in serum of PC patients grade III compared to grade II, (b) upregulation in miR-181a expression in serum of stage III compared to stage II.

Diagnostic performance of lncRNA ZNF674-AS1, miR-181a, STAT3 and SOCS4

The diagnostic potential of studied markers was evaluated using ROC analysis (Figure 4). Serum lncRNA ZNF674-AS1 demonstrated the highest diagnostic accuracy, with an area under curve (AUC) of 0.99 with (cut off values of ≤ 0.62, AUC=0.99, 98.2% sensitivity and 100% specificity) (Figure 4a). Diagnostic performance was also observed for miR-181a (AUC = 0.88; cut-off value 1.42, 85.5% sensitivity, 100% specificity) (Figure 4b) and STAT3 (AUC = 0.96; cut-off 2.77, 96.4% sensitivity, 98.2% 272 specificity) (Figure 4d). Finally, serum SOCS4 levels yielded an AUC of 0.86 (cut-off value of ≤ 145.3 pg/mL, 67.3% sensitivity, 92.7% specificity) (Figure 4c) with (P value < 0.05) for all biomarkers.

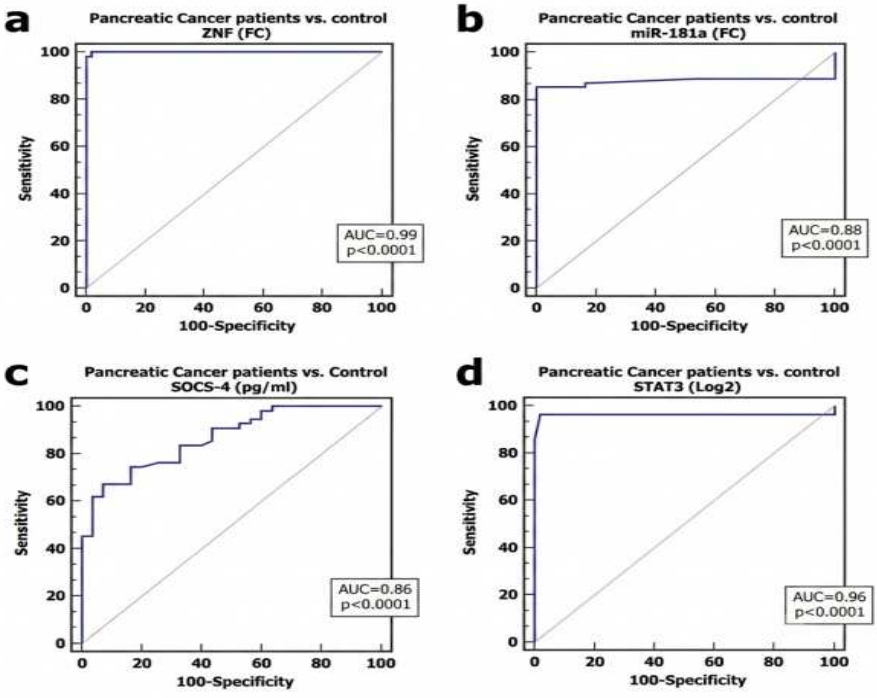


Figure 3: ROC curve analysis for lncRNA ZNF674-AS1, miR-181a, SOCS4 and STAT3 (a) showing cut off values of ≤0.62, (p value<0.001, AUC=0.99), 98.2% sensitivity and 100% specificity for lncRNA ZNF674-AS1, (b) cut off values of 1.42 (p value<0.001, AUC=0.88), 85.5% sensitivity and 100% specificity for miR-181a (c) cut off values of ≤145.3 pg/mL (p value<0.001, AUC=0.86), 67.3% sensitivity and 92.7% specificity for SOCS4 and (d) cut off values of 2.77 (p value<0.001, AUC=0.96), 96.4% sensitivity and 98.2% specificity for STAT3.

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DISCUSSION

Pancreatic carcinoma is considered the third most common type of cancer with a poor 5-year survival rate due to its high invasiveness and poor prognosis [16]. Numerous molecular interactions and signaling pathways are implicated in the development and progression of cancer pancreas [17]. Non-coding RNAs (ncRNAs) are pivotal players in regulation of gene expression, with special interest to miRNAs and lncRNAs [18, 19]. LncRNA ZNF674-AS1 was identified in the past decade and has been proven to exert a regulatory role in the development of several malignancies, as in lung cancer and in HCC [20, 21]. Members of the miR-181 family exhibit aberrant expression in a variety of tumor cells where they may function as either tumor-suppressive or oncogenic features [22]. Early findings have revealed that miR-181a promotes the invasion capability of pancreatic cancer [23]. STAT3 as one of the STAT family has established precancerous roles in various cancers, and STAT3 inhibitors are currently being evaluated in both pre-clinical and clinical studies [24]. Moreover, disruption of SOCS4 expression can result in uncontrolled JAK/STAT pathway activation and hence higher STAT3 levels [25].

In the present study, we aimed to evaluate the potential associations among lncRNA ZNF674- AS1, miR-181a, SOCS4 and STAT3 in the sera of patients with PC spotting the light on the potential role of lncRNA ZNF674-AS1in pancreas adenocarcinoma development through the proposed miR-181a/SOCS4/STAT3 regulatory axis. Interestingly, a recent study by Le et al, functionally validated the lncRNA ZNF674-AS1/miR-181a/ SOCS4 axis in cancer thyroid cultured cell and mice model by dual luciferase reporter assays demonstrating that lncRNA ZNF674-AS1 directly binds to and sequesters miR-181a, thereby inhibiting its action on target messenger RNAs thus increasing SOCS4 availability [10], Our results are consistent with this previously described approach and imply that the decreased serum expression of lncRNA ZNF674-AS1 may be linked to miR-181a-mediated reduction of SOCS4 in pancreatic cancer, even though our work did not specifically investigate these molecular interactions, further functional studies are required to confirm this proposed regulatory relationship. Another study found that inhibition of SOCS4 promoted proliferation and invasion of human renal cancer through dysregulation of JAK/STAT signaling pathway, decreased SOCS4 expression was linked to less inhibition of JAK/STAT signaling, which increased STAT3 activation and promoted oncogenic processes [15].

About 56.4% of PC participants were males, suggesting a higher prevalence of PC among men than women. and that agrees with Pijnappel et al. [26] who attributed the higher incidence of PC in men to both biological (sex-related) and gender-related factors. The reduced lncRNA ZNF674-AS1 expression in PC patients compared to control group goes in accordance with Zhang et al observations [7] who investigated lncRNA ZNF674-AS1 expression in 137 HCC tissue samples and demonstrated a marked reduction in its expression compared with adjacent non-tumorous tissues. Several studies have reported that lncRNA ZNF674-AS1 acts as a tumor suppressor. For example, reduced lncRNA ZNF674-AS1 expression has been associated with the development and progression of non-small cell lung cancer cells (NSCLC) [20]. However, contrasting evidence exists; for instance, inhibition of lncRNA ZNF674-AS1 has been shown to suppress neuroblastoma initiation [27]. This apparent contradiction highlights the dependent role of ncRNAs as they may act either as oncogenes or tumor suppressors, with their expression levels frequently fluctuating in a cancer type–specific manner [28].

In the present study, miR-181a expression was notably elevated in PC patients compared with the control group. Moreover, miR-181a expression increased significantly with disease progression, showing higher levels in grade III than grade II adenocarcinoma based on histopathological grading, as well as in Stage III compared with Stage II according to the TNM staging system. These findings agree with Gao et al. [29] who indicated that miR-181a promotes the invasive potential of pancreatic ductal adenocarcinoma (PDAC) cells. Furthermore, a decline in plasma miR-181a levels has been linked to better prognosis in PC patients [30].

Serum SOCS4 protein levels showed considerable decline in PC patients versus control group. Chen et al. [31] noted that targeting SOCS4 with miR-1290 activated both the JAK1/STAT3 and PI3K/AKT pathways, thereby promoting proliferation, invasion, and metastasis of lung adenocarcinoma cells. Similarly, previous studies have indicated that miR-876 specifically targets SOCS4, activating the STAT3 signaling pathway, allowing tumor immune evasion [32]. Accumulating evidence indicates that STAT3 plays a crucial role in cellular transformation and tumor initiation in PDAC. In particular, oncogenic Kirsten rat sarcoma virus (KRAS) mutations, present in approximately 90% of PDAC cases, have been shown to contribute to STAT3 hyperactivation [33]. Consistent with these findings, our present study revealed that STAT3 protein levels were considerably elevated in PC patients compared with the control group, supporting the potential involvement of enhanced STAT3 signaling in PDAC pathogenesis [34].

ROC analysis was performed to determine the potential diagnostic utility of the studied markers as non-invasive diagnostic tools for PC. Our results demonstrate that serum lncRNA ZNF674-AS1 and STAT3 show promising diagnostic accuracy, with high sensitivity and specificity, highlighting their potential as diagnostic biomarkers for PC. Collectively, the present study hypothesizes that a novel lncRNA ZNF674-AS1/ miR-181a/ SOCS4/STAT3 axis may be involved in the pathogenesis of PC, in which, decreased lncRNA ZNF674-AS1 relieves miR-181a inhibition, thus downregulating SOCS4 expression which in turn increases STAT3 expression. Furthermore, these molecules demonstrate as novel diagnostic biomarkers for PC, offering promising value for improving early detection and clinical management of the disease.

CONCLUSIONS

In conclusion, the present study demonstrated that lncRNA ZNF674-AS1 and serum SOCS4 protein levels were significantly downregulated in pancreatic cancer (PC)

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patients, whereas miR-181a and STAT3 expression levels were significantly upregulated compared with healthy controls. Furthermore, lncRNA ZNF674-AS1 and STAT3 showed promising potential as diagnostic biomarkers for PC. Notably, miR-181a expression was significantly higher in patients with grade III adenocarcinoma compared with those with grade II disease and in patients with stage III compared with stage II disease according to TNM staging, suggesting a possible association with pancreatic cancer progression. Collectively, these findings suggest that the ZNF674-AS1/miR-181a/SOCS4/STAT3 axis may have potential diagnostic and prognostic relevance in PC; however, additional in vitro and in vivo research are needed to determine the molecular basis of these interactions.

Conflicts of interest

The authors declare no competing interests.

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