Candidate Genes and Pathways in Ovarian Cancer: A Systematic Review and Integrated Bioinformatic Analysis

Authors: Geraldine Ardila MSc.[1] – Luz Dary Gutierrez MSc,PhD[2] – Carlos Maya MSc, PhD(c)[3]

1. Bioengineer. Fundación Universitaria de Ciencias de la Salud – FUCS, Hospital de San José and Universidad Central. Bogotá-Colombia.
2. Associate professor. Fundación Universitaria de Ciencias de la Salud – FUCS, Hospital de San José. Bogotá-Colombia.
3. Associate professor. Fundación Universitaria de Ciencias de la Salud – FUCS, Hospital de San José. Bogotá-Colombia.

Corresponding author: *Geraldine Ardila, gardila@fucsalud.edu.co*

The Festival of Genomics and Biodata Boston

Master's in Bioengineering and Nanotechnology

Introduction

Ovarian Cancer ranks 8th amongst the most common cancers in women across the world, resulting in 207252 deaths in the year 2020 (GLOBOCAN, 2020). The disease's high mortality can be attributed to the absence of specific symptoms in its early stages, thus decreasing the likelihood of an early diagnosis (Xiao et al., 2022). Prognosis is significantly determined by the stage at which the disease can be diagnosed, with the survival rate for each stage being: I (73–92%), II (45–55%), III (21%), and IV (6%) (Hossain et al., 2022).(Hossain et al., 2022).

The diagnostic methods are based on transvaginal ultrasound (TVUS), and blood screening for the cancer antibody 125 (CA125), and Human Epididymis Protein 4 (HE4) (Xiao et al., 2022). However, If many biomarkers are identified, it may be more possible to produce a test with higher sensitivity and specificity.

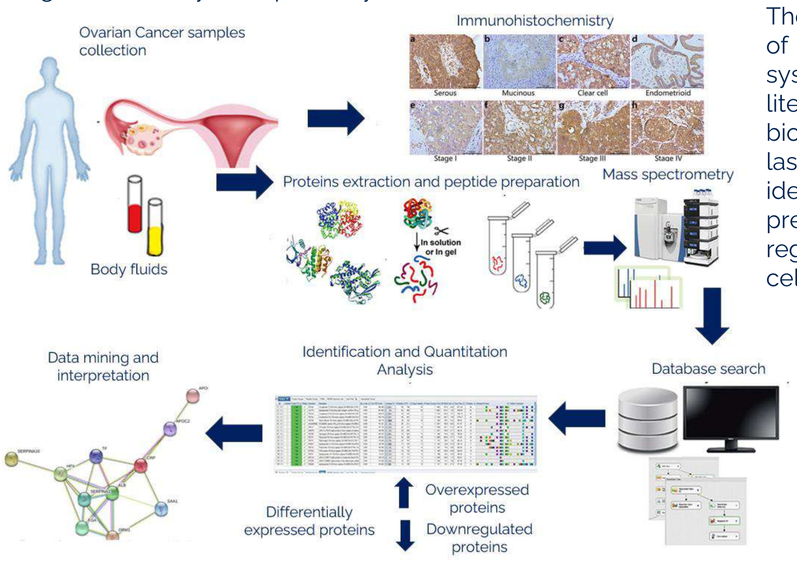
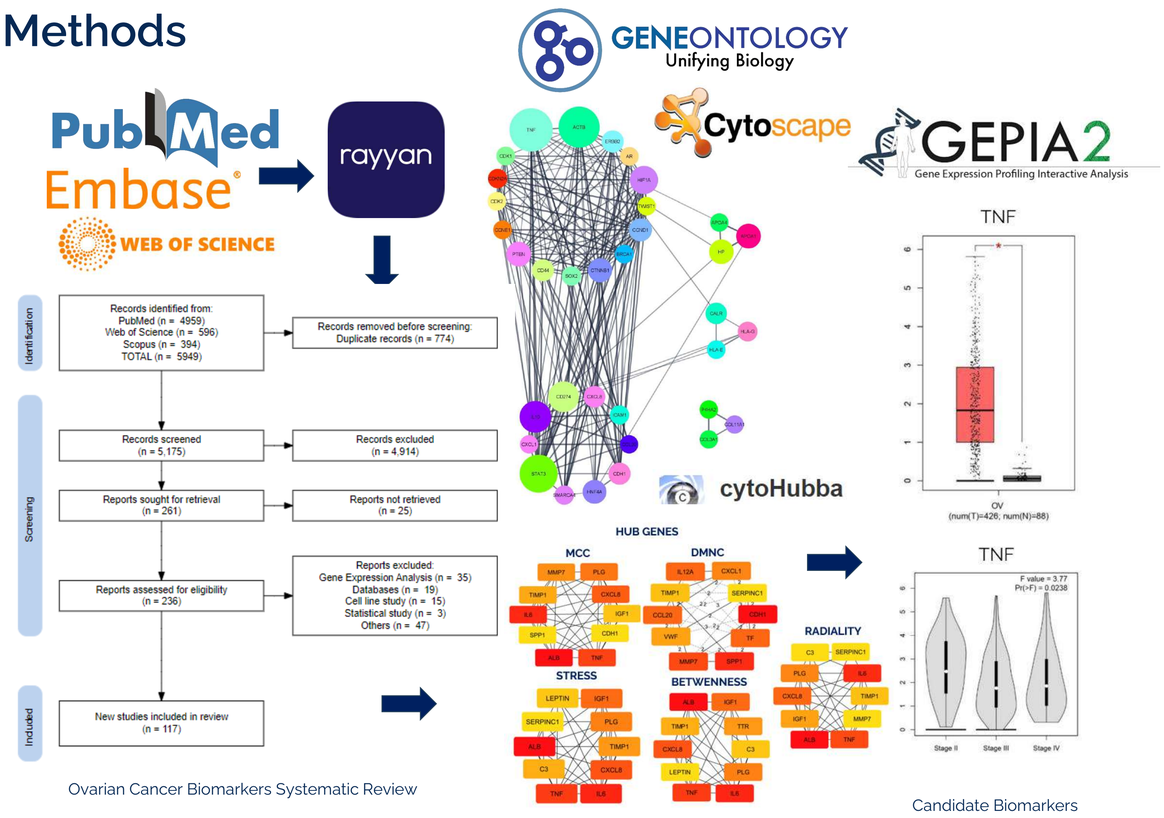


Figure 1. Ovarian Cancer Biomarkers Identification Process.

Therefore, the main **objective** of this study is to perform a systematic review of the literature to find relevant biomarkers identified in the last 6 years. Using the identified biomarkers, a prediction will be made regarding the associated cellular signaling pathways.

Methods



Results

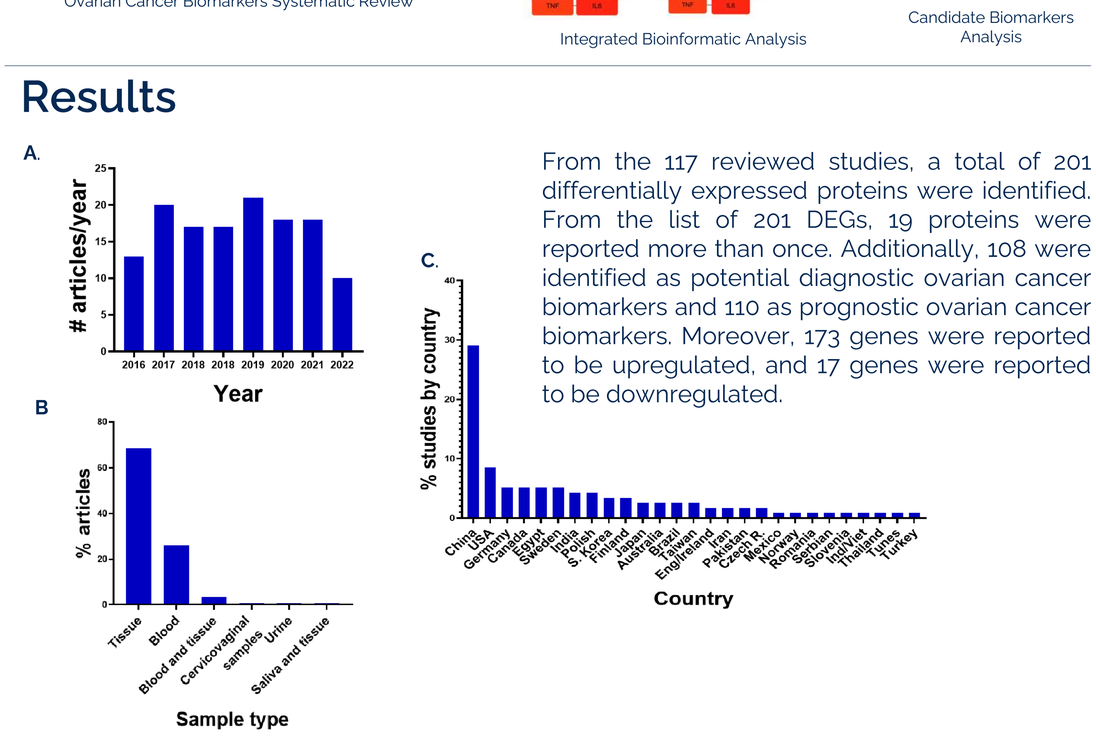


Figure 2. A. Distribution of selected studies across years. **B.** Distribution of studies according to samples used in study **C.** World distribution of selected studies.

From the 117 reviewed studies, a total of 201 differentially expressed proteins were identified. From the list of 201 DEGs, 19 proteins were reported more than once. Additionally, 108 were identified as potential diagnostic ovarian cancer biomarkers and 110 as prognostic ovarian cancer biomarkers. Moreover, 173 genes were reported to be upregulated, and 17 genes were reported to be downregulated.

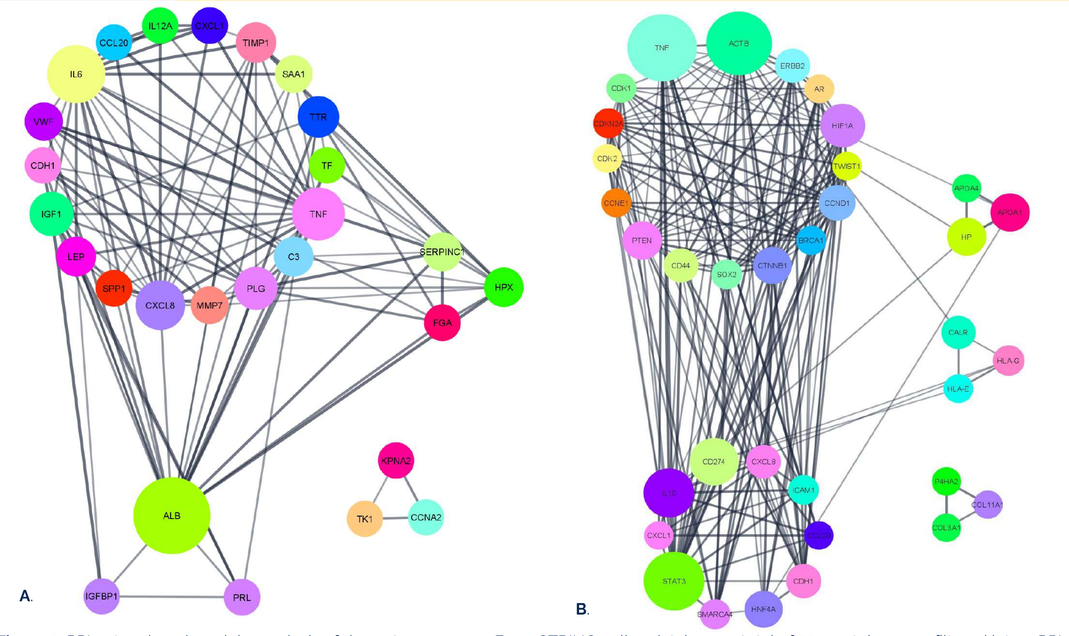


Figure 3. PPI network and modular analysis of downstream genes. From STRING online database, a total of 201 proteins were filtered into a PPI network complex. **A.** In Blood Samples. **B.** In Tumor Samples. Made with Cytoscape Software.

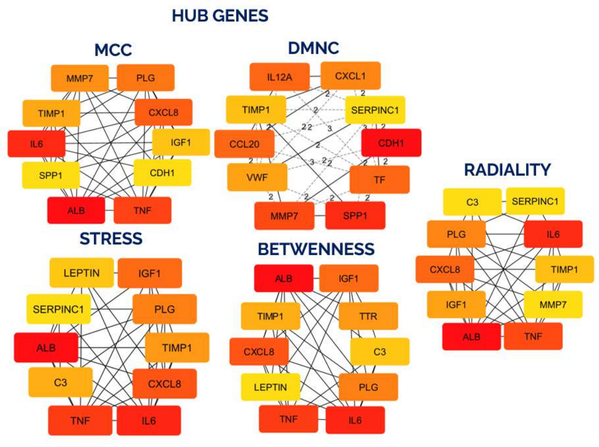


Figure 4. Hub genes identified by five different algorithms. From Blood Samples PPI Network.

The candidate biomarkers were chosen based on their significant involvement in biological processes (GO), and their high correlation in the candidate modules (hub genes) identified by different topological algorithms in cytoHubba. Maximal Clique Centrality (MCC), Density of Maximum Neighborhood Component (DMNC), Betweenness centrality, Radiality centrality, and Stress centrality.

Using the GEPIA2 database, an analysis of differentially expression was performed to compare with normal tissue samples with different OC stages.

Table 1. Hub genes chosen as candidates due to their significant expression in validation studies.

Type of Sample	Protein	Significant expression levels in normal samples VS ovarian cancer samples	Significant expression levels in ovarian cancer stages
Blood	**ALB**	✓	X
	CXCL8	✓	✓
	IGF1	X	X
	IL6	X	X
	TIMP1	X	X
	TNF	✓	✓
Tumor Tissue	ACTB	X	X
	CCND1	✓	X
	CTNNB1	X	✓
	HIF1A	X	X
	PTEN	X	X
	STAT3	X	✓

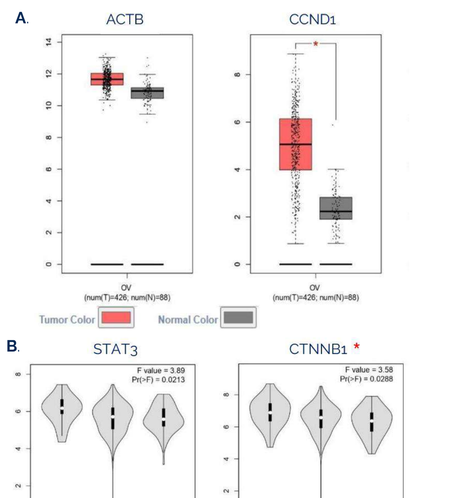


Figure 5. **A.** Hub genes validation of higher expression Red box was the cancer tissue group, gray was the normal tissue group. **B.** The expression levels of hub genes in ovarian cancer stages made with GEPIA2 database and asterisk represented $p < 0.01$.

Discussion

According to the type of sample, the candidate biomarker will have a different utility. Analysis of tumor tissue samples can show proteins involved in tumor development and their usefulness is important in prognosis and prediction of response to chemotherapy (Engqvist et al., 2019; Wang et al., 2019). Moreover, the analysis of blood and saliva samples could be useful for early diagnosis of the disease and included into clinical routine given their low invasiveness (Enroth et al., 2019). The identification of blood markers could precede the clinical manifestation of the disease, allowing preoperative differential diagnosis of ovarian tumors and reducing unnecessary surgical procedures, as well as improving patients' survival (Atallah et al., 2021; Swiatly et al., 2017; Ueland, 2017). For this reason, it is important to review and compile the information reported in the literature to show the most frequently reported proteins that can be analyzed in clinical samples of patients with OC or in the population at risk of this cancer (Kasimir-Bauer et al., 2020).

The strength of this systematic review is that includes studies from multiple cohorts and populations, however, the limitations were the incomplete listing of the differentially expressed genes in some of the studies as well as the classification on upregulated or downregulated genes. Also, the multiple techniques used by the studies affect the homogeneity of the obtained data. Finally, this systematic review added a new insight into the molecular mechanism of ovarian cancer.

Conclusions

The candidate biomarkers ALB, CCND1, CTNNB1, CXCL8, STAT3 and TNF, could be used in the future, either to make an earlier diagnosis improving patient prognosis and/or identification of signaling pathways that can be blocked by targeted therapies. This study highlights the importance of developing tests with higher sensitivity and specificity for the at-risk population, in order to detect OC at the earliest stage.

Bibliography

Xiao, Y., Bi, M., Guo, H., & Li, M. (2022). Multi-omics approaches for biomarker discovery in early ovarian cancer diagnosis. EBioMedicine, 79, 104001. https://doi.org/10.1016/j.ebiom.2022.104001

Hossain, K. R., Escobar Bermeo, J. D., Warton, K., & Valenzuela, S. M. (2022). New Approaches and Biomarker Candidates for the Early Detection of Ovarian Cancer. Frontiers in Bioengineering and Biotechnology, 10(February), 1–6. https://doi.org/10.3389/fbioe.2022.819183

Utkarsh, K., Kumar, A., Aditi, Khan, A., Nayyar, A., Haque, S., & Iqbal, S. (2022). Circulating and non circulating proteins and nucleic acids as biomarkers and therapeutic molecules in ovarian cancer. Genes and Diseases, xxxx. https://doi.org/10.1016/j.gendis.2022.07.004

Nebgen, D. R., Lu, K. H., & Bast, R. C. J. (2019). Novel Approaches to Ovarian Cancer Screening. Current Oncology Reports, 21(8), 75. https://doi.org/10.1007/s11912-019-0816-0

Engqvist, H., Parris, T. Z., Kovács, A., Nemes, S., Werner Rönnerman, E., De Lara, S., Biermann, J., Sundfeldt, K., Karlsson, P., & Helou, K. (2019). Immunohistochemical validation of COL3A1, GPR158 and PITHD1 as prognostic biomarkers in early-stage ovarian carcinomas. BMC Cancer, 19(1), 928.

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