CENTER OF EXCELLENCE FOR OPEN SCIENCE

Open Access

Email: ccbr@ceospublishers.com

CEOS Cancer Biology and Research

Research Article

15 Gene Signature as A Poor Prognostic Marker in Adrenocortical Carcinoma

Dominik Dabrowski

Department of Pathology, 23346Louisiana State University Health Sciences Center, Shreveport, LA, USA.

Received Date: January 06, 2022
Accepted Date: February 06, 2023
Published Date: February 08, 2023

***Corresponding Author**

Dominik Dabrowski, Department of Pathology, 23346Louisiana State University Health Sciences Center, Shreveport, LA, USA, Tel: 17186195421, E-mail: dabrowskidom@gmail.com

Citation

Dominik Dabrowski (2023) 15 Gene Signature as A Poor Prognostic Marker in Adrenocortical Carcinoma. CEOS Cancer Microbiol Res 1: 1-11

Abstract

Adrenocortical carcinoma, or Adrenal Cortical Carcinoma (ACC) is a rare malignant neoplasms originating of adrenal cortical tissue with an annual incidence rate of 1 to 2 cases per million individuals[1, 2]. The tumors have poor prognosis with 5 year disease free survival being 30% after complete resection in Stage I to III patients[3, 4]. We analyzed the data in The Cancer Genome Atlas of 1141 adrenocortical carcinoma individuals and derived correlated between the prognosis of an individual patients and genetic alterations in approximately 51,309 genes. We identified a set of top 15 genes which indicated poor prognosis for adrenocortical carcinoma individuals. Our analysis demonstrated the disease specific median survival for the patients of adrenocortical carcinoma was greater than 180 months, with 90% survival being 180 months, but with the alterations in the 15 signature genes the disease specific median survival was reduced to 39.5 months with p value less than 8 x 10 -9 with a sensitivity of 93%. In addition, our analysis of 15 signature genes demonstrates reduced overall survival, disease free survival and progression free survival in individuals having alterations in these 15 genes in adrenocortical carcinoma and indicate a possibility of using our 15 gene set signature in determining the prognosis of patients with adrenocortical carcinomas.

Keywords: adrenocortical carcinoma; neoplasm; signature gene; prognosis; survival

Introduction

Adrenal Cortical Carcinomas or adenoid cystic carcinomas of the adrenal gland are a rare malignant tumors originating from the cortical region of the adrenal cortex, with incidence rates approximately equally in both genders at a rate between 0.5 to 2 cases per million[1, 2]. These tumors can be hormonally active (40 to 60%) or inactive forms (30-45%)[5, 6]. Individuals with hormonally active ACC present with virilization, Cushing Syndrome and hypertension[6-10]. When inactive, the individuals present as gastrointestinal symptoms due to mass effect (in approximately 30% of all the ACCs) or are identified incidentally (in approximately 20% of the ACCs)[9, 11, 12]. The genes associated with adrenocortical carcinomas were previously identified by the study of familial diseases and there were association between ACC and germline p53 mutations in Li-Fraumeni syndrome and insulin like growth factor IGF2 in Beckwith-Weidmann syndrome[13-16]. Now with the advent of next generation sequencing, mutations in p53 and IGF2 have identified that are implicated in ACC tumorigenesis, in addition the genes involved in WNT signaling pathway like the proto-oncogene β-catenin (CTNNB1) and ZNRF3 (Zinc and ring finger protein 3) have also been implicated in ACC tumorigenesis[17].

Adrenocortical carcinoma is diagnosed mainly histologically, since radiologically, an ACC may be difficult to distinguish from an Adrenal Cortical Adenoma, as both present as encapsulated adrenal masses[18,19]. Although clues such as necrosis and a more heterogenous mass suggest ACC, but these are non-specific[20,21]. Grossly, observing an encapsulated, necrotic mass further increases suspicion of ACC[1,22]. On routine hematoxylin and eosin stain, ACCs are described as having pattern less sheets or nests of cells possessing fibrosis, necrosis, and even inflammatory cells[23-25]. The current standard for diagnosis on histology is known as the modified Weiss criteria and evaluates specimen for following features such as high nuclear grade, mitotic rate > 5 mitoses per 50 high powered (40x) fields , atypical mitotic figures , < 25% clear cells , diffuse architecture, necrosis, venous invasion, sinusoidal invasion and capsular invasion[26-28]. In order for the diagnosis of adrenocortical carcinoma to be confirmed the patient should have at least 3 out of 9 features of Weiss criteria[29]. The sensitivity and specificity of the diagnosis of ACC can be increased with the use of immunostains such as Ki67, p53, steroidogenic factor I (SF-1), insulin-like growth factor-II (IGF-II), cyclin E and β-catenin. Weiss score and Ki67 are also used as a prognostic markers in ACC patients[24, 30]. In general, higher Weiss score and Ki67 index over 7% are associated with poor prognosis in ACC[31-33]. However, since ACC is very rare cancer, the prognostic markers are infrequently studied. So we looked at the correlation between the genetic alterations and disease specific survival in the genomic data of the 1142 adrenocortical carcinoma tumors deposited in The Cancer Genome Atlas database (TCGA). The Cancer Genome Atlas database consists of genomic characterization of 7922 tumors from nearly 230 different studies[34]. Also the database has patient specific prognostic indicators like overall survival, disease free survival , progression free survival and disease-specific survival matched to individual patients, from whom the tumors have been derived[34-37]. The datasets in the TCGA database can be explored and analyzed using cbioportal which is a web-based platform designed by Memorial Sloan Kettering Cancer Centers Computational Biology Center, which enables the researchers to explore, visualize and analyze the data in the TCGA datasets[38-40].

Materials and Methods

The human gene list was downloaded from Ensembl genes 99 database using Human genes (GRCh38.p13 dataset)[41, 42]. The Cancer Genome Atlas database consists of genomic characterization of 1142 adrenocortical carcinoma tumors from nearly two different studies. The pan cancer atlas study consisted of 94 cases and the prognostic marker data was published in the literature [43], but the adenoid cystic carcinoma project study which had 1049 samples was deposited as a raw data in TCGA database[34]. We combined both the datasets and analyzed the mutational profile of each individual genes in 44924 gene set and determined whether each gene in our dataset is altered in the ACCs, number of cases in which the gene in altered, whether alteration is associated in reduced or increased survival and median overall survival associated with the alteration using cbioportal.org, which a web-based platform designed by Memorial Sloan Kettering Cancer Centers Computational Biology Center (Supplementary Table I). We identified 19536 genes in which the survival was altered. Out of 19536 genes which had altered survival 5236 genes were associated with reduced survival p value < 0.05. We selected 1607 genes with reduced survival and p value < 0.0005. And these genes were sub sorted depending on the number of cases in which the corresponding genes were altered and arranged in a decreasing order. Top 15 genes, with highest number of altered in greatest number of patients, were selected from this subset and analyzed using cbioportal.org platform for over survival (Table 1).

Table 1: List of 15 signature genes selected after analyzing 51,309 genes in 1141 ACC specimen dataset in TCGA atlas.

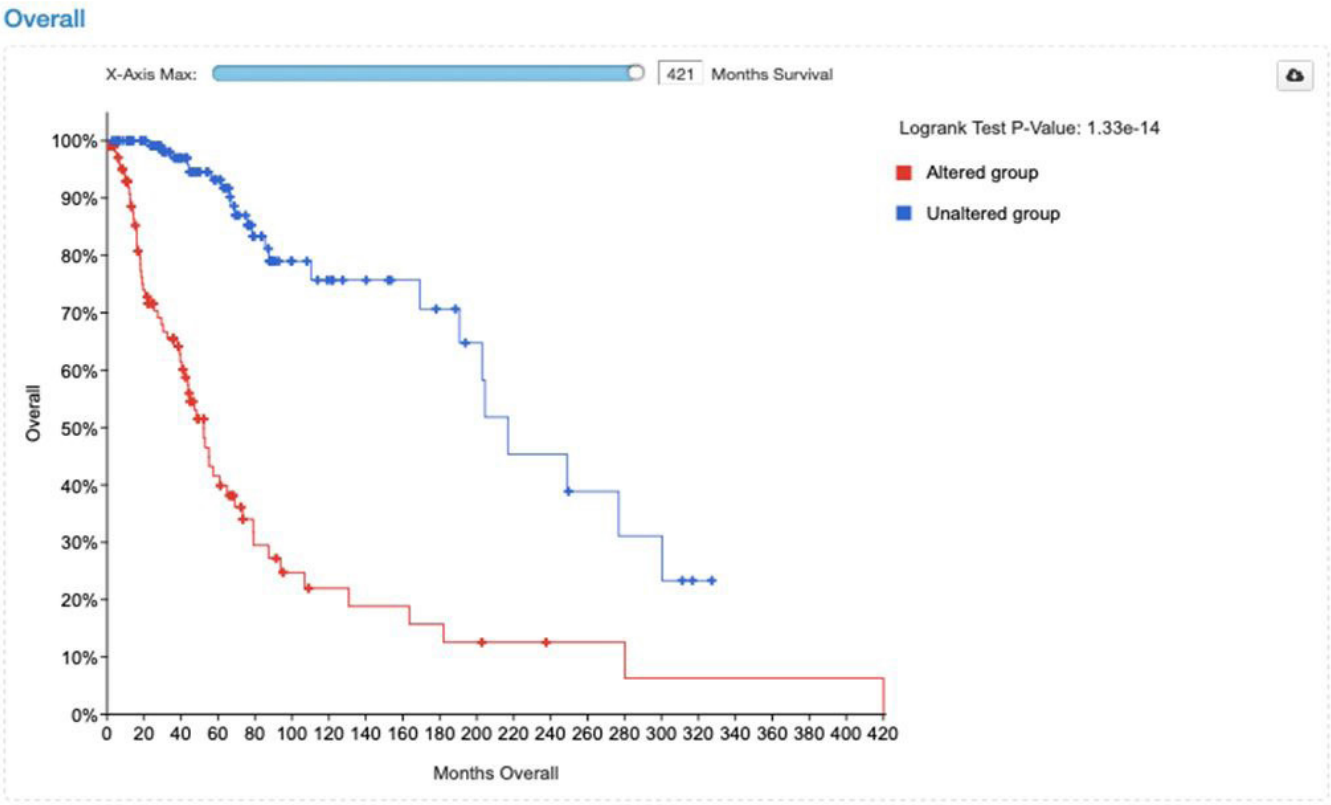
Gene name
NOTCH1
TP53
ZNRF3
LRP1
KIF5A
MDM2
LETMD1
MTOR
NOTCH3
RERE
SMARCC2
LDLR
HRNR
AVPR1A
PCDH15

Results

Our analysis picked up NOTCH1, TP53, ZNRF3, LRP1, KIF5A, MDM2, LETMD1, MTOR, NOTCH3, RERE, SMARCC2, LDLR, HRNR, AVPR1A and PCDH15 were the top 15 genes altered in highest number of patients, with alterations leading to reduced survival and p value less than 0.05. These genes were altered in 39% of the overall cases, that includes 49 out of 91 cases in TCGA Pan Cancer 2018 dataset and 395 out of 1049 cases in AACRF 2019 dataset. We observed an overall median survival of 52.7 months in altered group vs 217.09 months in unaltered group, with a sensitivity of 72% and p value less than 0.05 (Figure 1). The disease free median survival was 69.01 months in altered group vs > 153.63 months in unaltered group, with a sensitivity of 64.2% and p value less than 0.05 (Figure 2). The progression free median survival was 11.54 months in altered group vs > 153.63 months in unaltered group, with a sensitivity of 77% and p value less than 0.05 (Figure 3). The disease specific median survival was 39.58 months in altered group vs > 153.63 months in unaltered group, with a sensitivity of 93.1% and p value less than 0.05 (Figure 4).

Discussion

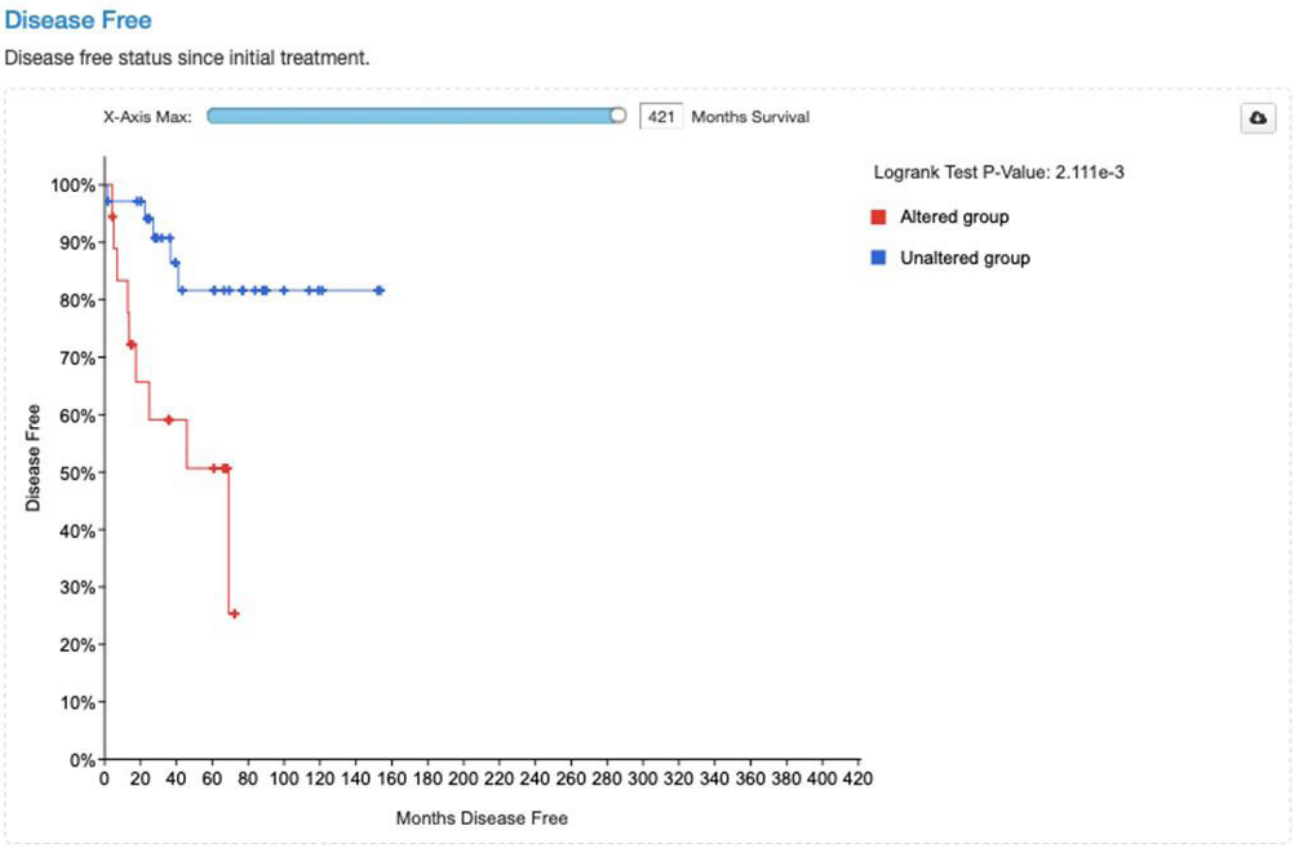
Our analysis picked up 15 gene signature which can act as prognostic signature in adrenocortical carcinoma. Our set of signature genes had a 93% sensitivity in identifying cases associated with reduced disease specific survival, but had lower sensitivity for progression free survival, disease free survival and overall survival. Since overall survival measures overall mortality (which can be influenced by other comorbid conditions)[44], whereas disease specific survival measures mortality rate due to a given disease[45, 46], the disease specific survival is a better indicator for determining the prognosis pattern[47, 48], and our set of signature genes are highly sensitive in identifying cases with poor disease specific survival. Moreover, our set of 15 genes belonged to 3 main MDM2-TP53 pathways, NOTCH signaling pathway and mTOR pathway (which are involved DNA damage response, cellular proliferation, apoptosis, angiogenesis and immune response) and deregulation of the pathways can give survival advantage to tumor cells and results in poor prognosis[49-53]. There are been small molecule modulators NOTCH and mTOR pathways under research and development and our set of signature genes might serve as a basis for identifying the individuals who are candidates to targeted therapy with these modulators[54, 55].



Overall median survival Altered group=52.7 months
Overall median survival Unaltered group= 217.09

Figure 1: Overall survival associated in individuals harboring ACC tumors having alterations in our 15 gene signature set vs overall survival in individuals harboring ACC tumors having no alterations in our 15 genes signature set.

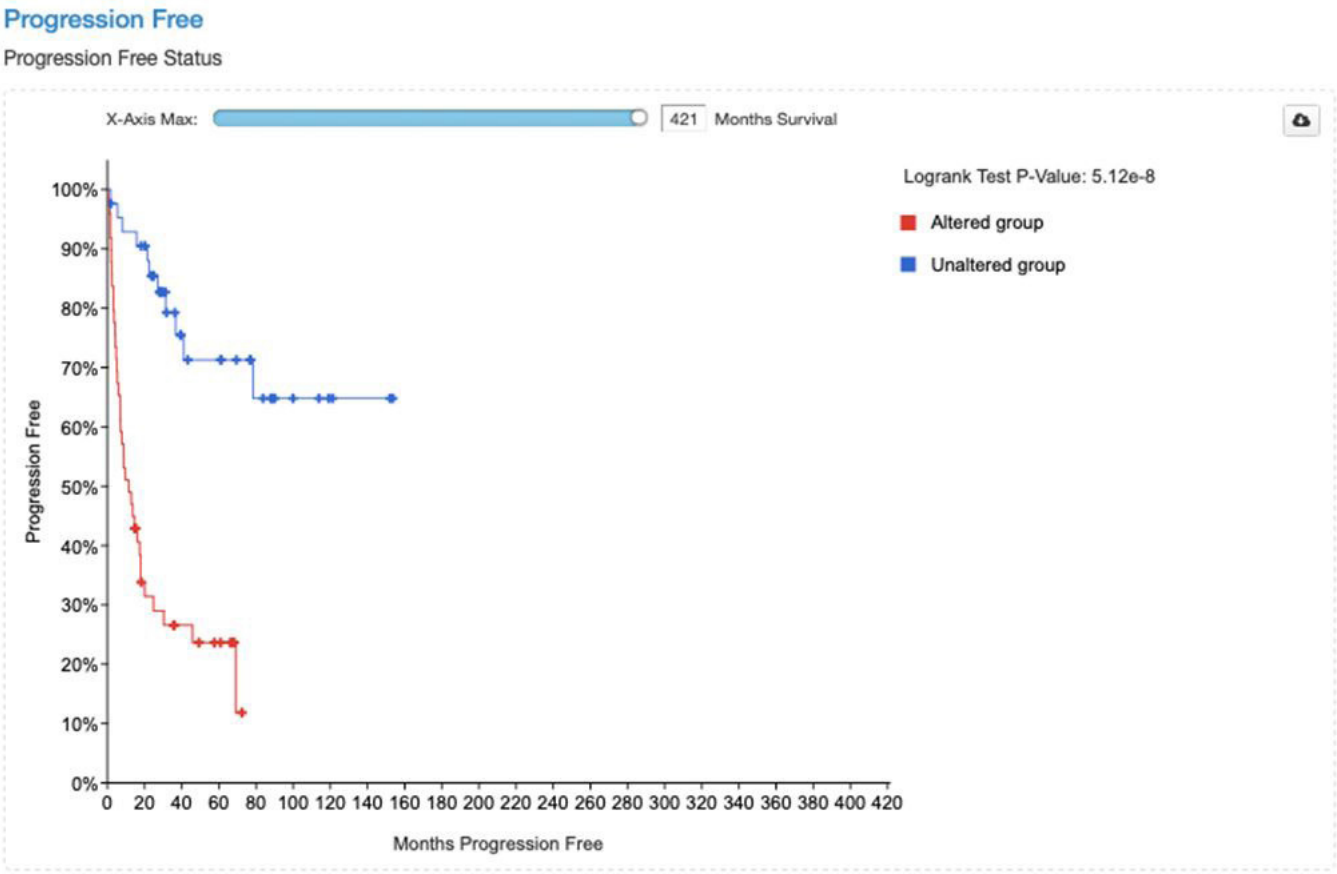
	Deceased	Surviving	Total
Altered Group (Positive)	61	45	106
Unaltered group (Negative)	23	106	129
Total	84	151	
Sensitivity =	**72.61904762**		
Specificity =	**70.1986755**		
Positive predictive value =	**57.54716981**		
Negative predictive value =	**82.17054264**		



Overall disease free survival Altered group=69 months
Overall disease free survival Unaltered group > 180 months

Figure 2: Disease free survival associated in individuals harboring ACC tumors having alterations in our 15 gene signature set vs disease free survival in individuals harboring ACC tumors having no alterations in our 15 genes signature set.

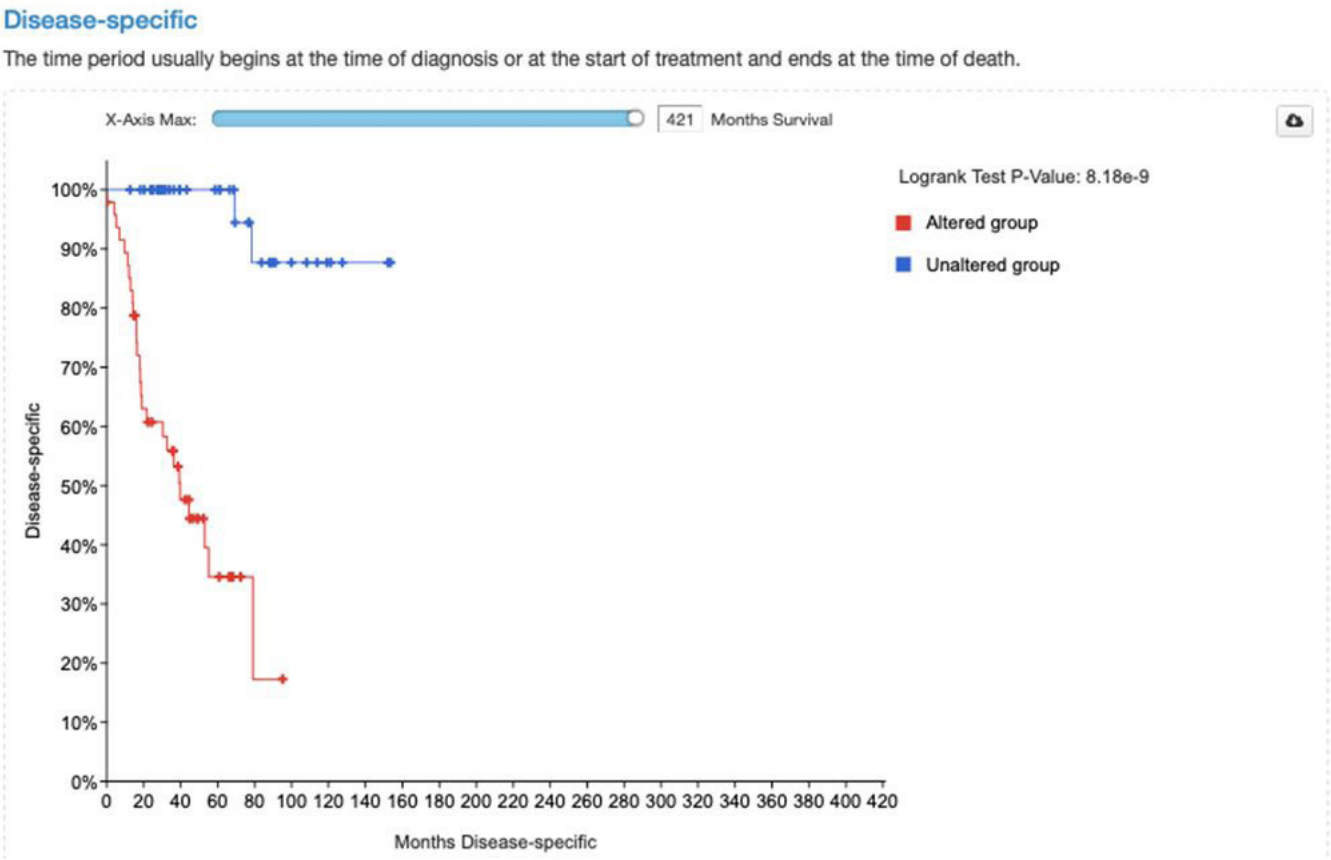
	No of cases recurred	No of cases with no recurrence	Total
Altered Group (Positive)	9	9	18
Unaltered group (Negative)	5	30	35
Total	14	39	
Sensitivity =	**64.28571429**		
Specificity =	**76.92307692**		
Positive predictive value =	**50**		
Negative predictive value =	**85.71428571**		



Overall progression free survival Altered group= 11.54 months
Overall progression free survival Unaltered group > 180 months

Figure 3: Progression free survival associated in individuals harboring ACC tumors having alterations in our 15 gene signature set vs progression free survival in individuals harboring ACC tumors having no alterations in our 15 genes signature set.

	No of cases progressed	No of cases with no progression	Total
Altered Group (Positive)	37	12	49
Unaltered group (Negative)	11	31	42
Total	48	43	
Sensitivity =	**77.08333333**		
Specificity =	**72.09302326**		
Positive predictive value =	**75.51020408**		
Negative predictive value =	**73.80952381**		



Overall Disease Specific Survival Altered group= 39.58 months
Overall Disease Specific Survival Unaltered group > 180 months

Figure 4: Disease specific survival associated in individuals harboring ACC tumors having alterations in our 15 gene signature set vs disease specific survival in individuals harboring ACC tumors having no alterations in our 15 genes signature set.

	No of cases deceased	No of cases survived	Total
Altered Group (Positive)	27	20	47
Unaltered group (Negative)	2	40	42
Total	29	60	
Sensitivity =	**93.10344828**		
Specificity =	**66.66666667**		
Positive predictive value =	**57.44680851**		
Negative predictive value =	**95.23809524**		

References

1. Else T, et al. (2014) Adrenocortical carcinoma. Endocrine reviews 35: 282-326.

2. Benassai G, et al. (2014) Adrenocortical carcinoma: what the surgeon needs to know. Case report and literature review. Int J Surg 1: S22-8.

3. Şişman P, et al. (2017) Adrenocortical carcinoma: Single centre experience. Turkish journal of urology 43: 462-9.

4. Ayala-Ramirez, M., et al. (2013) Adrenocortical carcinoma: clinical outcomes and prognosis of 330 patients at a tertiary care center. European journal of endocrinology 169: 891-9.

5. Libé, R (2015) Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment. Frontiers in cell and developmental biology 3: 45.

6. Ahmed AA, et al. (2020) Adrenal cortical carcinoma: pathology, genomics, prognosis, imaging features, and mimics with impact on management. Abdominal Radiology 45: 945-63.

7. Huang CJ. et al. (2013) Adrenocortical carcinoma initially presenting with hypokalemia and hypertension mimicking hyperaldosteronism: a case report. BMC research notes 6: 405.

8. Jairath A and BS Aulakh (2014) Adrenocortical carcinoma in pregnancy: A diagnostic dilemma. Indian journal of urology: IJU: journal of the Urological Society of India 30: 342-4.

9. Lee JA and QY Duh (2009) Functioning and Non-functioning Adrenal Tumors, in General Surgery, K.I. Bland, et al., Editors. Springer London: London. 1687-98.

10. Hallanger-Johnson JE (2020) Systemic therapy for adrenocortical carcinoma: a review. AME Medical Journal 5.

11. Symeonidis D et al. (2013) Adrenocortical carcinoma presenting with signs of acute abdomen. Case reports in surgery 132726.

12. Stigliano A, et al. (2012) Current and emerging therapeutic options in adrenocortical cancer treatment. Journal of oncology 408131.

13. Lodish M (2017) Genetics of Adrenocortical Development and Tumors. Endocrinology and metabolism clinics of North America 46: 419-33.

14. Else T (2012) Association of adrenocortical carcinoma with familial cancer susceptibility syndromes. Molecular and cellular endocrinology 351: 66-70.

15. Pittaway JFH and L Guasti (2019) Pathobiology and genetics of adrenocortical carcinoma 62: R105.

16. Almeida MQ et al. (2018) Primary malignant tumors of the adrenal glands. Clinics 73.

17. Wilmouth J et al. (2019) WNT pathway deregulation in adrenal cortex tumorigenesis. Current Opinion in Endocrine and Metabolic Research 8.

18. Wang C et al. (2014) Distinguishing adrenal cortical carcinomas and adenomas: a study of clinicopathological features and biomarkers. Histopathology 64: 567.

19. Bharwani N et al. (2011) Adrenocortical carcinoma: the range of appearances on CT and MRI. AJR Am J Roentgenol 196: W706-14.

20. Albano D et al. (2019) Imaging features of adrenal masses. Insights into imaging 10: 1.

21. Herr K et al. (2014) Imaging of the adrenal gland lesions. Radiologia brasileira 47: 228-39.

22. Scarpelli M et al. (2004) Handling and Pathology Reporting of Adrenal Gland Specimens. European Urology 45: 722-9.

23. Abstracts and Case Studies from the College of American Pathologists (2019) Annual Meeting (CAP19). Archives of Pathology & Laboratory Medicine 143: e2-26.

24. Mondal S et al. (2013) Histopathological study of adrenocortical carcinoma with special reference to the Weiss system and TNM staging and the role of immunohistochemistry to differentiate it from renal cell carcinoma. Journal of Cancer Research and Therapeutics 9: 436-41.

25. Nakamura Y et al. (2015) Adrenocortical carcinoma: review of the pathologic features, production of adrenal steroids, and molecular pathogenesis. Endocrinol Metab Clin North Am 44: 399-410.

26. Jain M et al. (2010) Weiss criteria in large adrenocortical tumors: A validation study. Indian Journal of Pathology and Microbiology 53: 222.

27. Wanis KN and R Kanthan (2015) Diagnostic and prognostic features in adrenocortical carcinoma: a single institution case series and review of the literature. World Journal of Surgical Oncology 13: 117.

28. de Krijger RR and TG Papathomas (2012) Adrenocortical neoplasia: evolving concepts in tumorigenesis with an emphasis on adrenal cortical carcinoma variants. Virchows Archiv: an international journal of pathology 460: 9-18.

29. Wanis KN and R Kanthan (2015) Diagnostic and prognostic features in adrenocortical carcinoma: a single institution case series and review of the literature. World journal of surgical oncology 13: 117.

30. Libé R (2015) Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment. Frontiers in Cell and Developmental Biology 3.

31. Choi YM et al. (2016) Clinicopathological Features Associated with the Prognosis of Patients with Adrenal Cortical Carcinoma: Usefulness of the Ki-67 Index. Medicine 95: e3736.

32. Jouinot A and J Bertherat (2018) MANAGEMENT OF ENDOCRINE DISEASE: Adrenocortical carcinoma: differentiating the good from the poor prognosis tumors. Eur J Endocrinol 178: R215-r230.

33. Crona J and F Beuschlein (2019) Adrenocortical carcinoma — towards genomics guided clinical care. Nature Reviews Endocrinology 15: 548-60.

34. Tomczak KP Czerwińska and M Wiznerowicz (2015) The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. Contemporary oncology (Poznan, Poland) 19: A68-77.

35. Cancer Genome Atlas Research Network (2017) Electronic address, w.b.e. and N. Cancer Genome Atlas Research, Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. Cell 169: 1327-41.e23.

36. Liu J et al. (2018) An Integrated TCGA Pan-Cancer Clinical Data Resource to Drive High-Quality Survival Outcome Analytics. Cell 173: 400-16.e11.

37. Ni J et al. (2020) Screening the Cancer Genome Atlas Database for Genes of Prognostic Value in Acute Myeloid Leukemia. Frontiers in Oncology 9.

38. Cerami E et al. (2012) The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer discovery 2: 401-4.

39. Lee JS (2016) Exploring cancer genomic data from the cancer genome atlas project. BMB reports 49: 607-11.

40. Jonckheere N and I Van Seuningen (2018) Integrative analysis of the cancer genome atlas and cancer cell lines encyclopedia large-scale genomic databases: MUC4/MUC16/MUC20 signature is associated with poor survival in human carcinomas. Journal of Translational Medicine 16: 259.

41. Aken BL et al. (2016) The Ensembl gene annotation system. Database (Oxford).

42. Ruffier M et al. (2017) Ensembl core software resources: storage and programmatic access for DNA sequence and genome annotation. Database (Oxford).

43. Zheng S et al. (2016) Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma. Cancer cell 29: 723-36.

44. Patnaik JL et al. (2011) The influence of comorbidities on overall survival among older women diagnosed with breast cancer. Journal of the National Cancer Institute 103: 1101-11.

45. Mariotto AB et al (2014) Cancer survival: an overview of measures, uses, and interpretation. Journal of the National Cancer Institute. Monographs 145-86.

46. Choi J et al. (2019) Health Indicators Related to Disease, Death, and Reproduction. Journal of preventive medicine and public health = Yebang Uihakhoe chi 52: 14-20.

47. Feng SS et al. (2019) Clinical characteristics and disease-specific prognostic nomogram for primary gliosarcoma: a SEER population-based analysis. Scientific reports 9: 10744.

48. Wang J et al. (2020) Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. Cancer medicine 9: 361-73.

49. Silkenstedt E et al. (2019) Notch1 signaling in NOTCH1-mutated mantle cell lymphoma depends on Delta-Like ligand 4 and is a potential target for specific antibody therapy. Journal of experimental & clinical cancer research: CR 38: 446.

50. Moens U and A Macdonald (2019) Effect of the Large and Small T-Antigens of Human Polyomaviruses on Signaling Pathways. International journal of molecular sciences 20: 3914.

51. Alsahafi E et al. (2019) Clinical update on head and neck cancer: molecular biology and ongoing challenges. Cell Death & Disease 10: 540.

52. Stallone G et al. (2019) mTOR and Aging: An Old Fashioned Dress. International journal of molecular sciences 20: 2774.

53. Sanz G et al. (2019) Inhibition of p53 inhibitors: progress, challenges and perspectives. Journal of Molecular Cell Biology 11: 586-99.

54. Sorrentino C, A Cuneo and G Roti (2019) Therapeutic Targeting of Notch Signaling Pathway in Hematological Malignancies. Mediterranean journal of hematology and infectious diseases 11: e2019037.

55. Chamcheu JC et al. (2019) Role and Therapeutic Targeting of the PI3K/Akt/mTOR Signaling Pathway in Skin Cancer: A Review of Current Status and Future Trends on Natural and Synthetic Agents Therapy. Cells 8.

CEOS
CENTER OF EXCELLENCE FOR OPEN SCIENCE

CEOS is an growing Open Access Publisher with diverse peer reviewed journals supported by Aca demic Editors, Scholars, Physicians, Instructors,

CEOS Publishers follow strict ethical standards for publication to ensure high quality scientific studies, credit for the research participants. Any ethical issues will be scrutinized carefully to maintain the integrity of literature.

CEOS Publishers believes scientific integrity and intellectual honesty are essential in all scholarly work. As an upcoming publisher, our commitment is to protect the integrity of the scholarly publica-tions, for which we take the necessary steps in all aspects of publishing ethics.

All the articles published in CEOS Publisher journals are licensed under Creative CommonsCC BY 4.0 license, means anyone can use, read and dow-nload the article for free. However, the authors reserve the copyright for the published manuscript.