



## RESEARCH ARTICLE

### ASSOCIATION BETWEEN PRIMARY SITE OF MELANOMA AND SURVIVAL OF U.S. ADULT PATIENTS

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#### Manuscript Info

##### Manuscript History

Received: 26 November 2016  
 Final Accepted: 27 December 2016  
 Published: January 2017

##### Key words:-

Melanoma, Melanocyte, Primary site, Prognosis, Survival.

#### Abstract

**Introduction:** Melanoma is the most dangerous form of skin cancer. The National Cancer Institute estimated that there would be 76,100 new invasive melanoma cases and 9,710 deaths from melanoma in the US in 2014. Anatomic location was identified as a significant prognostic factor in patients with primary cutaneous melanoma (CM) by several investigators.

**Objectives:** The aim of this study is to assess the relationship between primary site of melanoma and survival in a large US adult population.

**Materials & methods:** We analyzed 227,509 US melanoma patients from the SEER (Surveillance, Epidemiology, and End Results Program Registry) from 1973 to 2011. We excluded duplicate cases. We compared the primary site and survival by using Kaplan-Meier curves. Hazard ratio (HR) were determined by unadjusted and adjusted Cox-regression model.

**Results:** In the unadjusted model, the primary anatomical site was significantly associated with survival. Melanoma patients who had a primary site as an overlapping lesion of skin (the tumor overlaps the boundaries of two or more adjacent anatomical sites) were 10 times more likely to die within 5 years of diagnosis compared to patients with non-overlapping lesions located on the head or neck (HR= 10.7, 95% CI=10.3 - 11.1). After we adjusted for age at diagnosis, gender, race, ethnicity and stage at diagnosis, patients with overlapping lesion of skin still had lower chance of surviving more than 5 years as compared to patients with non-overlapping head and neck lesions, followed by trunk (HR= 3.5, 95% CI= 3.3 - 3.6 and HR=1.2, 95% CI= 1.2 - 1.3, respectively).

**Conclusions:** Overlapping lesion of skin had the worst prognosis followed by trunk lesions, while lesions located at upper limbs & shoulders had better prognosis. Clinical correlation and timely diagnosis of primary melanoma sites might improve survival and prognosis in this population

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## Introduction:-

Melanoma is the most dangerous form of skin cancer that represents 4.6% of all new cancer cases in the United States. The National Cancer Institute estimated that there would be 76,100 new invasive melanoma cases and 9,710 deaths from melanoma in the United States in 2014 [1,2]. Anatomic location was identified as a significant prognostic factor in patients with primary cutaneous melanoma (CM) by several investigators [3,4,5,6]. Understanding the role of anatomic site in melanoma survival is important for public health messages on skin awareness and sun protection. Moreover, because the role of screening in melanoma is considered important for early detection [7,8]. The location often has been classified into four anatomic regions: head and neck, trunk, and the upper and lower extremities [9,10,11,12]. But some authors have tried to subdivide anatomic location into higher and lower risk sites according to recurrence or survival rates [5,13,14,15]. Cutaneous head and neck melanomas (CHNM) constitute 12-21% of melanomas diagnosed annually [16,17]. CHNM have poorer outcomes relative to melanomas of other sites (MOS) [18,19,20]. Extremity lesions have generally been associated with a more favourable prognosis than trunk and head and neck lesions, even when adjusted for tumour type and thickness [21,22]. Other authors have confirmed that the anatomical location is a prognostic factor, but have demonstrated a poor prognosis in association with other areas, such as the BANS region (upper back, posterior arm, neck and posterior scalp) [23].

## Objectives:-

The aim of this study is to assess the relationship between primary site of melanoma and survival in a large US adult population.

## Literature Review:-

Warren H. Tseng et al argued that Tumor Location Predicts Survival in Cutaneous Head and Neck Melanoma. An analysis of the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute of all patients with CHNM diagnosed from 1988 to 2006. Kaplan-Meier survival curves depicting overall survival (OS) and melanoma specific survival (MSS) dependent on location of tumor. Result shown that ten-year overall survival was 55.1% for all patients with cutaneous head and neck melanoma. For tumors of the scalp/neck, 10-year rates of overall survival was 57.2%. 10-year overall for cutaneous head and neck melanoma (CHNM) at sites other than the scalp/neck was 55.6%. the author concluded that Patients with melanomas of the scalp/ neck have poorer OS and MSS and those with lip melanomas have poorer MSS. These anatomic areas should not be overlooked when performing skin examinations [24].

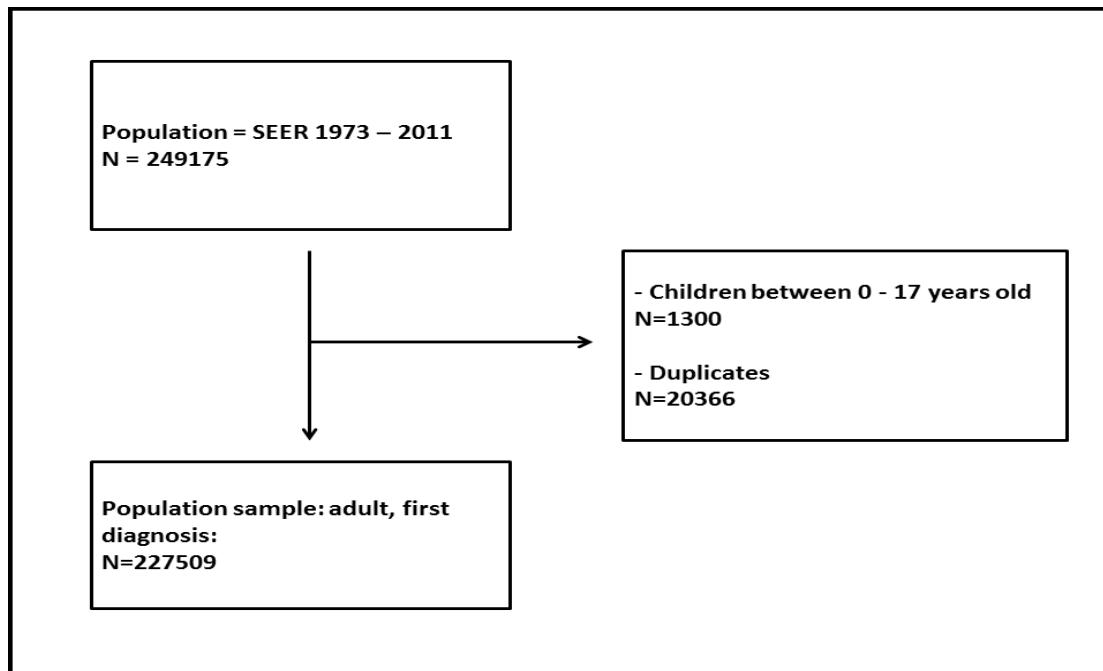
Claus Garbe, et al discussed Prognostic Classification of Anatomic Location of Primary Cutaneous Melanoma. In a series of 5093 patients with invasive primary cutaneous melanoma followed from 1970 to 1988 at four university centers in Germany who were investigated using the multivariate Cox proportional hazard model to analyze the importance of anatomic location for survival probability. The back and breast (thorax), upper arm, neck, and scalp (TANS regions) were identified as high risk sites as the univariate 10-year survival rates for primary CM showed significant site-related differences ranging from 63.4% (scalp), 68% (back) to 87.7% (lower arm), 82.4% (lower leg). The author concluded that the Anatomic location was confirmed as an independent prognostic factor for patients with primary cutaneous melanoma. The TANS regions were identified as high risk sites, and the lower trunk, thigh, lower leg, foot, lower arms, hands, and face were identified as intermediate sites [25].

H. M. SHAW, et al discussed Influence of Site of Lesion and Age of Patient in the Female Superiority in Survival. Statistical analyses of differences between survival rates were carried out by the Logrank method. Observed and expected differences were analyzed for significance by the chi-square test with one degree of freedom. final group comprised 753 patients (362 men and 391 women). Result showed that Melanoma of extremities had better prognosis than axial melanoma with 5-yr survival (<1.5mm thick) of 85.7% in men and 96.8 % in women. as opposed to axial melanoma 5-yr survival (<1.5mm thick) of 75.7% in men and 84.3% in women. The author concluded that The association between decline in prognosis with increasing age and decline in proportion of thin lesions with increasing age was much closer in men than women. In men and women matched by age, site, and thickness of primary lesions, women with very thick tumors still survived longer [26].

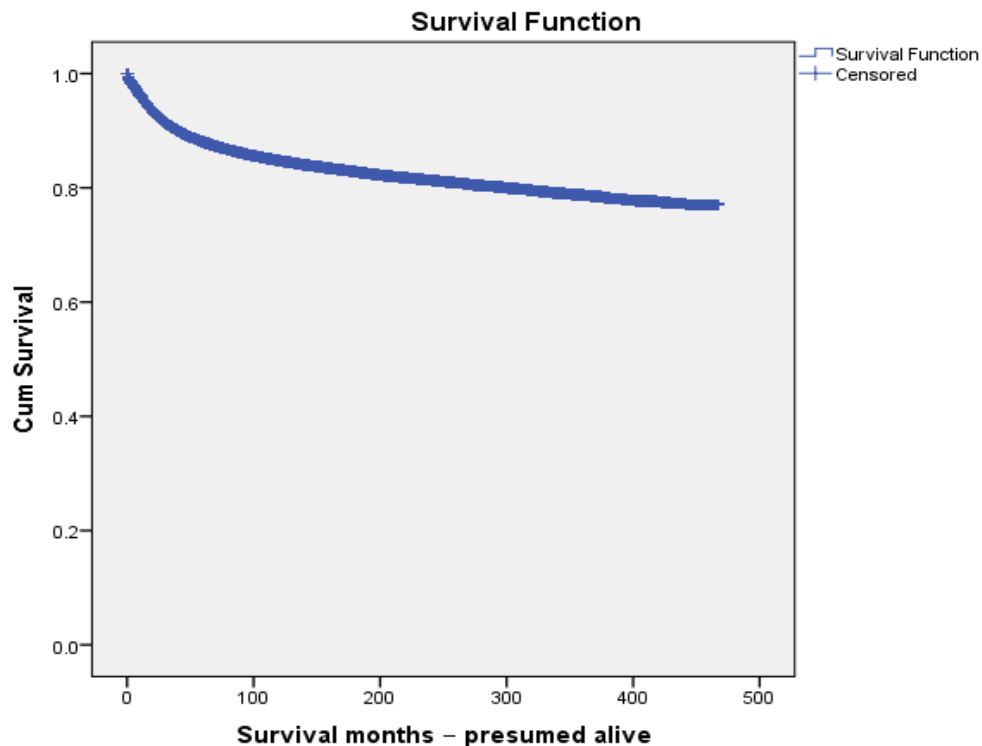
## Material & Method:-

In this study our population was 249175 US melanoma patients from the SEER (Surveillance, Epidemiology, and End Results Program Registry) during the 1973 to 2011 period. We excluded 20366 patients as duplicated cases and

1300 patients younger than 18 years old. The final group was 227509 US melanoma patients, we analyzed them using SPSS [Figure 1]. We used Kaplan-Meier curves to compare primary sites and survival with 5 years interval [Figure 2]. Hazard ratio (HR) were determined by unadjusted and adjusted Cox-regression model.



**Figure 1:-**Selection of melanoma patient from SEER database 1973 - 2011



**Figure 2:-** Kaplan Meier curve of survival time for adult melanoma patients in US (1973-2011)

## Result and Discussion:-

Patients with primary lesions located at trunk contributed the highest number of patients by 64457 followed by head and neck by 58138 Patients. Patients with Overlapping lesions were 14948 as the smallest group.[Figure 3]

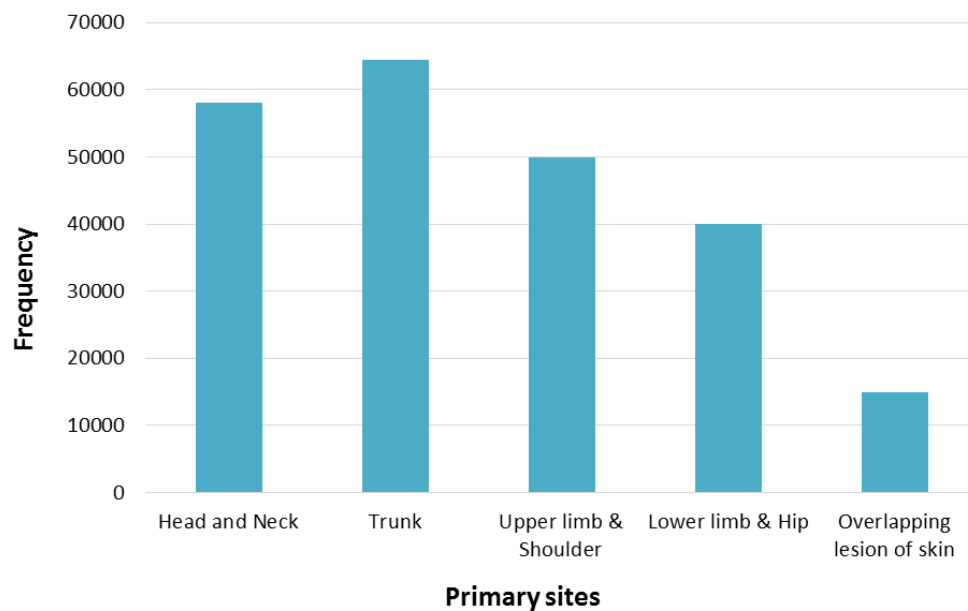
The Mean Age of patients with primary site at Head & neck lesion are older (65.5) which is higher than other lesion. Men have higher percentage of overlapping lesion of skin and skin NOS (81.7%) while women contribute higher percentage of lower limb & hip lesion (70.4%). Most of melanoma patients are white (97.1%). Most of the melanoma patients are Non- Spanish-Hispanic-Latino (97.7%).Patients with overlapping lesion and Skin NOS diagnosed at late stage in contrast to other lesions. [Table 1]

Patients who survived 5 years or less are older (61.3) compare to those who survived more than 5 years. Patient with primary sites of melanoma located at lower limb/hip and trunk have higher percentage in more than 5 year category (63.9% and 63.5% respectively). While patients with primary site defined as overlapping lesion of skin and skin NOS have the lower percentage (26.5%) of surviving more than 5 years. Women diagnosed with melanoma have better higher percentage of surviving after 5 years compared with men (64.8% and 53.8% respectively). Patients diagnosed at early stage (63.7%) have more probability of surviving 5 years or more than those at late stage (36.3%). [Table 2]

In our unadjusted model the primary site was significantly associated with the survival. Melanoma patients whose primary site was overlapping lesion of skin/skin NOS are 10 times more likely to die due to melanoma compared to patients with lesions at head/neck (HR= 0.772). Women are 60% less likely to die from melanoma compared with men. Patients diagnosed at late stage are have worse prognosis in comparison to those diagnosed at early stage (HR= 11.229).

After we adjusted for age and stage at diagnosis, gender, race and ethnicity, overlapping lesion of skin/skin NOS and lower limb/hip were highly associated with unfavorable prognosis of melanoma compared to head/neck (HR= 3.500 and HR=1.900 respectively). Women are still less likely to die from melanoma compared with men (H=0.600). Patients who have the worst prognosis for melanoma are those diagnosed at late stage (HR=8.900) and white patients (HR=1.200). [Table 3]

Less than 10% of overlapping lesions patients survived 60 months. Around 43% of trunk and lower limbs and hip patients survived 60 months.Upper limb and shoulder and head and neck patients had the highest percentage of surviving 60 months by more than 50%. [Figure 4]



**Figure 3:-** Number of patients per primary sites

**Table1:** Characteristics of melanoma patients I by primary site in US, (SEER 1973-2011)

Characteristics	Head & neck	Trunk	Primary Site Upper limb & Shoulder	Lower limb & Hip	Overlapping lesion of skin & skin NOS <sup>c</sup>	Sig <sup>a</sup>
	N (%)	N (%)	N (%)	N (%)	N (%)	
<b>Age at diagnosis in years (mean, SD)<sup>b</sup></b>	(65.5, ±16.1)	(53.9, ±16.3)	(57.4, ±16.5)	(52.7, ±17.0)	(48.7, ±17.3)	<0.001
<b>Gender</b>						<0.001
Male	39237 (67.5)	41242 (64.0)	24847 (49.7)	11819 (29.6)	12209 (81.7)	
Female	18901 (32.5)	23215 (36.0)	25135 (50.3)	28165 (70.4)	2739 (18.3)	
<b>Race</b>						<0.001
White	55826 (98.2)	61330 (97.9)	47689 (98.3)	37194 (95.5)	13251 (89.9)	
Black	375 (0.7)	630 (1.0)	404 (0.8)	1070 (2.7)	1132 (7.7)	
Other <sup>d</sup>	638 (1.1)	664 (1.1)	483 (0.9)	676 (1.7)	362 (2.5)	
<b>Ethnicity</b>						<0.001
Non-Spanish-Hispanic-Latino	57029 (98.1)	63329 (98.2)	49076 (98.2)	38732 (96.9)	14002 (93.7)	
Spanish-Hispanic-Latino	1109 (1.9)	1128 (1.8)	906 (1.8)	1252 (3.1)	5341 (2.3)	
<b>Stages<sup>e</sup></b>						<0.001
Early	50601 (91.3)	56228 (91.0)	44099 (92.5)	32301 (89.5)	1378 (26.0)	
Late	4832 (8.7)	5558 (9.0)	3552 (7.5)	3771 (10.5)	3912 (74.0)	
<b>Mortality</b>						<0.001
Alive or dead of other cause	43788 (90.2)	51522 (89.0)	40660 (91.8)	32094 (88.2)	5099 (36.7)	
Dead	4778 (9.8)	6378 (11.0)	3642 (8.2)	4286 (11.8)	8797 (63.3)	

<sup>a</sup> P-value was calculated based on Chi-square unless otherwise specified<sup>b</sup> Significant of age was calculated based on ANOVA test<sup>c</sup> NOS: not otherwise specified<sup>d</sup> Other (Race): American Indian/AK Native, Asian/Pacific Islander<sup>e</sup> Satge has 9.4% missing**Table 2:** Association between Survival and Age, Gender , Race, Ethnicity, Stage and mortality in melanoma patients

Characteristics	Survival (years)			
	≤ 5 years	> 5 years		p-value <sup>a</sup>
	N (%)	N (%)		
<b>Age at diagnosis in years (mean,SD) <sup>b</sup></b>	(61.3 , ± 17.8)	(54.1 , ± 16.3)		< 0.001
<b>Primary site</b>				< 0.001
Head & Neck	26287 (45.2)	31851 (54.8)		
Trunk	23554 (36.5)	40903 (63.5)		
Upper limb & shoulder	19045 (38.1)	30937 (61.9)		
Lower limb & Hip	14425 (36.1)	25559(63.9)		
Overlapping lesion of skin and skin NOS <sup>c</sup>	10983(73.5)	3965(26.5)		
<b>Gender</b>				< 0.001

Male	59767 (46.2)	69587 (53.8)		
Female	34527 (35.2)	63628 (64.8)		
<b>Race</b>			< 0.001	
White	88527 (41.1)	126763 (58.8)		
Black	2088 (57.8)	1523 (42.2)		
Other <sup>d</sup>	1268 (45.6)	1510 (54.4)		
<b>Ethnicity</b>			< 0.001	
Non-Spanish-Hispanic-Latino	91662 (41.3)	130505 (58.7)		
Spanish-Hispanic-Latino	2632 (49.3)	2709 (50.7)		
<b>Stages</b>			< 0.001	
Early	67086 (36.3)	117521 (63.7)		
Late	13770 (63.7)	7855 (36.3)		
<b>Mortality</b>			< 0.001	
Alive or dead of other cause	58171 (33.6)	114992 (66.4)		
Dead	21164 (75.9)	6717 (24.1)		

<sup>d</sup> Other (Race): American Indian/AK Native, Asian/Pacific Islander

<sup>a</sup> P-value was calculated based on Chi-square unless otherwise specified

<sup>b</sup> Significant of age was calculated based on T test

<sup>c</sup> NOS: not otherwise specified

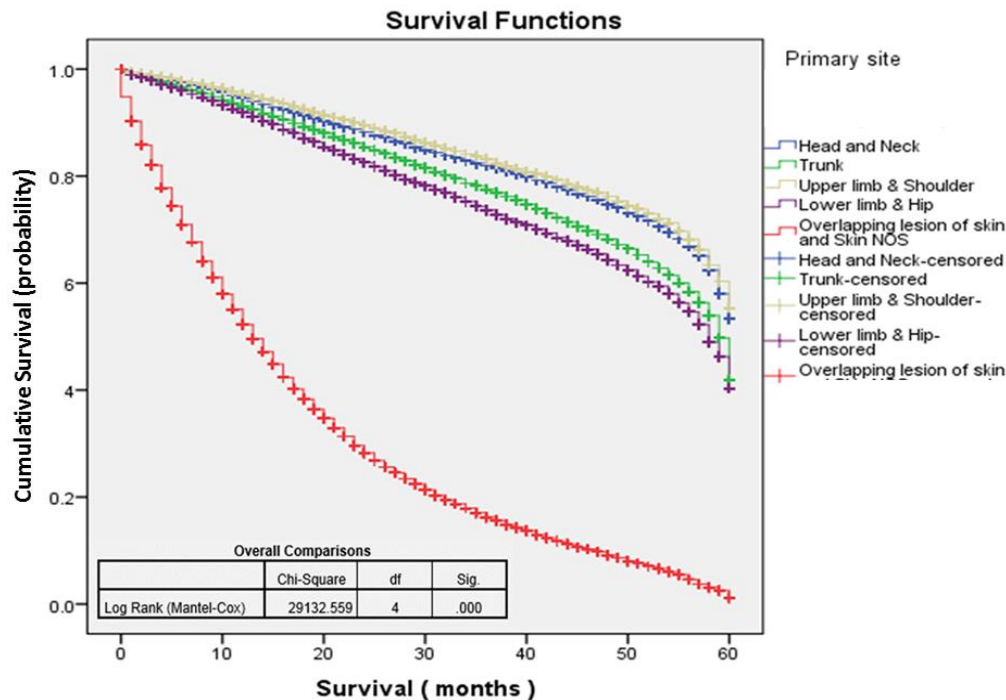
**Table 3:** Unadjusted and Adjusted associations between hazard ratio and characteristics of melanoma patients

Characteristics	Survival (months)			
	Unadjusted		Adjusted	
	HR (95% CI)	p-value	HR <sup>a</sup> (95% CI)	p-value
<b>Primary site</b>				
Head & Neck	Ref		Ref	
Trunk	1.017 (0.979 - 1.056)	0.391	1.245 (1.193-1.298)	<0.001
Upper limb & shoulder	0.772 (0.739 - 0.806)	<0.001	0.906 (0.863-0.951)	<0.001
Lower limb & Hip	1.081 (1.037 - 1.126)	<0.001	1.196 (1.138-1.257)	<0.001
Overlapping lesion of skin and skin NOS <sup>b</sup>	10.723 (10.347 - 11.112)	<0.001	3.507 (3.325-3.698)	<0.001
<b>Age at diagnosis in years</b>	0.999 (0.998 - 1.000)	0.02	1.022 (1.021-1.023)	<0.001
<b>Gender</b>				
Male	Ref		Ref	
Female	0.369 (0.386 - 0.407)	<0.001	0.671 (0.650-0.693)	<0.001
<b>Race</b>				
White	0.274 (0.259 - 0.289)	<0.001	1.265 (1.108-1.445)	<0.001
Black	Ref		Ref	
Other <sup>c</sup>	0.452 (0.408 - 0.500)	<0.001	1.100 (0.918-1.304)	0.315
<b>Ethnicity</b>				
Non-Spanish-Hispanic-Latino	0.517 (0.487 - 0.548)	<0.001	0.952 (0.861-1.053)	0.339
Spanish-Hispanic-Latino	Ref		Ref	
<b>Stages</b>				
Early	Ref		Ref	
Late	11.229 (10.902 - 11.566)	<0.001	8.968 (8.687-9.258)	<0.001

<sup>a</sup>HR: Hazard Ratio

<sup>b</sup>NOS: not otherwise specified

<sup>c</sup> Other (Race): American Indian/AK Native, Asian/Pacific Islander



**Figure 4:-**Survival curve of primary sites (N=94294)

### Conclusions:-

This study have shown a very obvious difference in survival between the primary sites. Overlapping lesion of skin had the worst prognosis followed by trunk lesions while upper limb & shoulder lesions have a better prognosis. Timely diagnosis of primary melanoma sites will improve survival and prognosis of this population.

### Acknowledgments:-

We would like to thank Florida International University (FIU), Dr. Suliman Aba Al-Khail, Dr. Khalid Alqumaizi, Dr. Juan Zevallos, and Grettel Castro for their support and help.

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