ISSN: 2158-284X Volume 10, Number 8, August 2019

Scientific Research Publishing

International Journal of Clinical Medicine

ISSN: 2158-284X

www.scirp.org/journal/ijcm

Journal Editorial Board

ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
http://www.scirp.org/journal/ijcm

International Journal of Clinical Medicine, 2019, 10, 395-420
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Table of Contents

Volume 10 Number 8 August 2019

Pregnancy Outcome among Women with Sickle Cell Disease in a Tertiary Health Institution in Abakaliki: A Retrospective Case-Control Study

J. I. Nwafor, D.-P. C. Ugoji, C. C. Ibo, B. I. Onwe, V. J. U. Onuchukwu, C. N. Obi, V. O. Obi……395

The Relevance of Serum Cystatin C Level of Different Classification of Atrial Fibrillation

Y. Q. Duan, J. H. Xu, W. Hu, P. Li, R. Li……404

Septic Superficial Femoral Vein Thrombophlebitis Causing Pulmonary Emboli and Respiratory Failure: Case Report and Review of the Literature

Z. Fayad, P. Guentert, E. Rissler, N. Zackariya, S. Patel, A. Sualeh, M. Al-Fadhl, S. Zackariya, G. Wiarda, M. Martin, J. Lake, S. Philbrick, M. Walsh……413

International Journal of Clinical Medicine (IJCM)
Journal Information

SUBSCRIPTIONS

The *International Journal of Clinical Medicine* (Online at Scientific Research Publishing, www.SciRP.org) is published monthly by Scientific Research Publishing, Inc., USA.

Subscription rates:
Print: $79 per issue.
To subscribe, please contact Journals Subscriptions Department, E-mail: sub@scirp.org

SERVICES

Advertisements
Advertisement Sales Department, E-mail: service@scirp.org

Reprints (minimum quantity 100 copies)
Reprints Co-ordinator, Scientific Research Publishing, Inc., USA.
E-mail: sub@scirp.org

COPYRIGHT

PRODUCTION INFORMATION

For manuscripts that have been accepted for publication, please contact:
E-mail: ijcm@scirp.org

International Journal of Clinical Medicine, 2019, 10, 395-403
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Pregnancy Outcome among Women with Sickle Cell Disease in a Tertiary Health Institution in Abakaliki: A Retrospective Case-Control Study

Johnbosco Ifunanya Nwafor*, Darlington-Peter Chibuzor Ugoji, Chukwunenye Chukwu Ibo, Blessing Idzuinya Onwe, Victor Jude Uchenna Onuchukwu, Chuka Nobert Obi, Vitus Okwuchukwu Obi

Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
Email: *nwaforjohnbosco97@gmail.com

How to cite this paper: Nwafor, J.I., Ugoji, D.-P.C., Ibo, C.C., Onwe, B.I., Onuchukwu, V.J.U., Obi, C.N. and Obi, V.O. (2019) Pregnancy Outcome among Women with Sickle Cell Disease in a Tertiary Health Institution in Abakaliki: A Retrospective Case-Control Study. *International Journal of Clinical Medicine*, **10**, 395-403.
https://doi.org/10.4236/ijcm.2019.108032

Received: July 6, 2019
Accepted: August 9, 2019
Published: August 12, 2019

Abstract

Background: Sickle cell disease (SCD) is associated with an increased risk of medical complications during pregnancy and they constitute a very high-risk group with associated increased maternal and perinatal morbidity and mortality especially in a low resource setting. **Objective:** To determine the pregnancy outcomes among women with sickle cell disease delivered at Alex Ekwueme Federal University Teaching Hospital, Abakaliki. **Materials and methods:** This was a 7-year retrospective case-control study undertaken from January 2012 to December 2018 that compared pregnancy outcomes among women with and without haemoglobinopathy in pregnancy managed at Alex Ekwueme Federal University Teaching Hospital, Abakaliki (AEFUTHA). The statistical analysis was done using SPSS version 22. **Results:** The incidence of SCD in pregnancy was 6.9 per 1000 deliveries. The age distribution of the women ranged from 18 to 45 years of age with a mean of 26.4 ± 2.4 years. The incidence of stillbirth was higher in women with HbSS when compared with HbSC but this difference did not reach statistical significance (P = 0.05). Live birth rate was higher in women with HbAA genotype when compared with those with SCD. Caesarean section rate was higher among women with SCD when compared with control (SS versus AA, P = 0.004; SC versus AA, P < 0.0001). Babies of mothers with HbSS and HbSC have significantly lower mean birth weight when compared with those of mothers with HbAA (SS versus AA, P = 0.0007; SC versus AA, P < 0.0001). Similarly maternal genotype has a significant effect on other adverse fetal outcomes such as Apgar scores < 7 at 5 minutes and preterm delivery. Women with SCD had higher incidence of pregnancy-induced hypertension and preeclampsia when compared with control. Maternal genotypes have no significant effect on other maternal complications. There was no maternal death in this study. **Conclu-**

sion: This study showed that the maternal mortality in SS and SC patients in pregnancy was not different from those of HbAA women in our hospital, although other maternal and fetal outcomes were still poor among women with SCD when compared with women without SCD.

Keywords

Pregnancy, Outcome, Sickle Cell Disease, Pregnancy, Abakaliki

1. Introduction

Sickle cell disease (SCD) is associated with an increased risk of medical complications during pregnancy and they constitute a very high-risk group with associated increased maternal and perinatal morbidity and mortality [1]-[7].

Sickle cell disease is common in the tropics and particularly so among the black race. The incidence in Nigeria is up to 3% of the population and about 25% may be carriers of haemoglobinopathies [1]. The haemoglobinopathies commonly encountered in pregnancy in Nigeria are SS or SC [1]. Sickle cell disease is common in present day obstetric practice because the advances in medical care have led to more girls having this condition surviving to childbearing age [2].

Pregnant women with SCD are known to be at high risk of obstetric complications and perinatal mortality as well as sickle cell-related complications [3]. The maternal and fetal complications include antepartum and postpartum painful crises, pulmonary complications, anemia, preeclampsia, eclampsia, premature delivery with associated risks, and intrauterine growth restriction (IUGR). In addition, pregnant women with SCD are at an increased risk of sickle cell crisis, urinary tract infections, gestational diabetes, pneumonia, and anemia [1]-[10].

Studies from developed countries have shown that there is a significant improvement in pregnancy outcome and that these women are able to complete pregnancy successfully if they are given appropriate prenatal care [4]. Unfortunately, no such improvement has yet been observed in sub-Saharan countries, which have the highest prevalence of SCD and reported rates of maternal mortality exceeding 9% [5] [6] [7] [8] [9]. Lack of adequate management during pregnancy is thought to be the major factor responsible for the poor maternal and fetal outcomes among women with SCD in sub-Saharan Africa compared with developed countries [11].

Currently, there is no Sickle cell clinic dedicated to active management of SCD during pregnancy in Abakaliki. Examining the possible complications in pregnancy associated with SCD may provide insight into the management of SCD pregnancies and it will help to provide for advocacy for establishment of such clinic in the different geopolitical zones of the country. The aim of this study was to identify association between SCD in pregnancy and the occurrence of adverse

maternal and fetal outcomes at Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Southeast Nigeria. Determining maternal and perinatal outcomes among pregnant women with SCD will highlight the reproductive health burden of SCD on maternal and infant health in Abakaliki, which may contribute to the basis for reducing the maternal and fetal mortality in our locality.

2. Materials and Method

This was a 7-year retrospective case-control study undertaken from January 2012 to December 2018 at the Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State, Nigeria. Pregnant women with SCD (HbSS or HbSC genotypes) who received antenatal care and gave birth at the department of obstetrics and gynecology were compared with pregnancies among women without hemoglobinopathies (control). The controls were women without haemoglobinopathies who matched SCD parturients with regards to age, parity and gestational age at delivery. The exclusion criteria were multiple pregnancies, incomplete or unavailable medical records, and presence of co-morbidity such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). The hospital numbers of the eligible women during the study period were retrieved from the admission register in the Antenatal ward. Then, the case notes were retrieved from the Medical Records Department of the hospital using the hospital numbers. A proforma containing information on the maternal age, parity, gestational age at delivery and haemoglobin concentration before labour and 48 hour post delivery was used to extract information from the case notes. Data regarding pregnancy outcome (miscarriage, stillbirth, live birth, early neonatal death), mode of delivery (live birth), outcome of live birth (birthweight, Apgar score <7 at 5 minutes). In addition, complications such as gestational hypertension (pregnancy-induced hypertension, pre-eclampsia, eclampsia), haemorrhage (antepartum and postpartum), gestational diabetes, retained placenta, uneventful pregnancies, sickle cell-related complications (painful crises, acute chest syndrome, urinary tract infection) and maternal death were also noted. The approval for the study was sought for and obtained from the Research and Ethics Committee of the hospital.

Statistical analysis: The data was entered and analyzed using SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean (standard deviation) or as a percentage with range, as appropriate. The effect of SCD on pregnancy was compared using Pearson Chi-square (χ^2) or one-way analysis of variance where appropriate to determine statistical differences between the groups of women (SCD and control). Multivariate logistic regression was used to control for confounding factors. A p-value < 0.05 was considered significant.

3. Results

There were 23,450 deliveries during the study period of which 164 (0.69%) were

women with SCD. The cases were 98 women with HbSS and 68 with HbSC genotype, whereas the control group was 160 randomly selected women with HbAA with a complete record to match the SCD group in terms of age, gravidity, and parity.

Table 1 showed the socio-demographic and obstetrics characteristics of study participants. The age distribution of the women ranged from 18 to 45 years of age with a mean of 26.4 ± 2.4 years. The majority of the women were between 25 and 34 years of age. There were no significant difference in the mean age of women with SCD and the control group (P = 0.86). A majority of the HbSS women (44%) were nulliparas (58%) compared with control group (33.1%), (P < 0.001). However, there was no significant difference in parity among HbSC and HbAA women. Overall, the mean haemoglobin concentration before labour and 48 hours following delivery were lower among women with SCD when compared with the control group (Mean haemoglobin before labour; HbAA = 10.6 ± 2.4 versus HbSS = 8.4 ± 0.8 and HbSC = 9.6 ± 1.5; Mean Haemoglobin 48 hours post-delivery; HbAA = 9.2 ± 2.8 versus HbSS = 6.9 ± 1.3 and HbSC = 8.2 ± 1.8).

The comparison of pregnancy outcomes between SCD women and HbAA women is shown in Table 2. The incidence of miscarriage was higher among women with HbSS genotype when compared with other genotypes. Four (4.1%)

Table 1. Characteristics of pregnant women with sickle cell disease (HbSC and HbSS) and control (HbAA).

Variable	HbSS (N = 98)	HbSC (N = 66)	HbAA (N = 160)
Age (years)			
18 - 24	28 (28.6)	16 (24.2)	47 (29.4)
25 - 34	56 (57.1)	33 (50)	78 (48.8)
≥35	14 (14.3)	17 (25.8)	35 (21.8)
Parity			
Nulliparous	44 (44.9)	28 (42.4)	53 (33.1)
Primiparous	35 (35.7)	23 (34.8)	46 (28.8)
Multiparous	19 (19.4)	15 (22.8)	61 (38.1)
Gestational age at delivery			
≤27	4 (4.1)	0 (0)	0 (0)
28 - 30	2 (2)	1 (1.5)	1 (0.6)
31 - 32	6 (6.1)	4 (6.1)	5 (3.1)
33 - 34	9 (9.2)	6 (9.1)	10 (6.3)
35 - 37	11 (11.2)	14 (21.2)	24 (15)
38 - 39	56 (57.1)	34 (51.5)	88 (55)
40 - 42	10 (10.3)	7 (10.6)	32 (20)
Mean haemoglobin concentration (g/dl)			
Before labour	8.4 ± 0.8	9.6 ± 1.5	10.6 ± 2.4
48 hour post delivery	6.9 ± 1.3	8.2 ± 1.8	9.2 ± 2.8

Table 2. Comparison of pregnancy outcome in sickle cell disease and control (HbAA).

Variable	HbSC	HbSS	HbAA	SS versus SC		SS versus AA		SC versus AA	
				χ^2	P-value	χ^2	P-value	χ^2	P-value
Total pregnancies (n)	66	98	160						
Pregnancy outcome, n (%)									
Miscarriage	0 (0)	4 (4.1)	0 (0)	-	-	-	-	-	-
Stillbirth	6 (9.1)	20 (20.4)	2 (1.3)	3.79	0.05	28.6	1.43	8.41	0.004
Live birth	60 (90.9)	74 (75.5)	158 (98.7)	4.2	0.08	36.2	<0.0001	8.31	0.003
Early neonatal death	2	3	3	0.05	0.82	0.93	0.34	0.39	0.53
Mode of delivery (live birth)									
Vaginal	43 (71.9)	58 (78.4)	145 (91.8)	43.81	0.54	8.26	0.004	14.81	<0.0001
Caesarean section	17 (28.1)	16 (21.6)	13 (8.2)						
Outcome of live birth (n)	60	74	158						
Birthweight									
Mean ± SD	2.9 ± 0.6	2.3 ± 0.4	3.2 ± 0.7	-	<0.0001	-	0.0007	-	<0.0001
Weight < 2.5 kg, n (%)	24 (40)	10 (13.5)	8 (5.1)	12.28	<0.0001	5.03	0.02	42.38	<0.0001
Apgar score < 7 at 5 minutes	8 (13.3)	6 (8.1)	14 (8.9)	0.97	0.33	0.03	0.84	0.96	0.33
Gestational age at delivery									
Preterm (<37 weeks)	20 (33.3)	21 (21.4)	19 (11.9)	0.38	0.54	9.45	0.002	13.44	<0.0001
Mean ± SD	37.6 ± 1.4	37.1 ± 1.2	38.6 ± 2.1	-	0.03	-	<0.0001	-	0.0008

women had miscarriage among women with HbSS. There were no miscarriages recorded among women with genotypes HbSC and HbAA. More stillbirths occurred in women with haemoglobinopathy when compared with control group. The incidence of stillbirth was higher in women with HbSS when compared with HbSC but this difference did not reach statistical significance (P = 0.05). Live birth rate was higher in women with HbAA genotype when compared with those with heamoglobinopathy. There was no significant different in live birth rate among women with HbSS and HbSC (P = 0.08). Mode of delivery differ significantly between women with sickle cell haemoglobinopathy when compared with control (SS versus AA, P = 0.004; SC versus AA, P < 0.0001). There was no significant difference in the mode of delivery when parturients with HbSS were compare with women with HbSC (P = 0.54). Maternal genotype has a significant effect on the mean fetal birth weight. Babies of mothers with HbSS and HbSC have significantly lower mean birth weight when compared with those of mothers with HbAA (SS versus AA, P = 0.0007; SC versus AA, P < 0.0001). Also the birth weight of babies born to women with HbSS was significantly lower than those of babies born to mothers with HbSC (P < 0.0001). Similarly maternal genotype has a significant effect on other adverse fetal outcomes such as Apgar scores < 7 at 5 minutes and preterm delivery.

Table 3 shows comparison of complications during pregnancy in the three genotypes. There were significant genotype differences in pregnancy-induced

Table 3. Comparison of pregnancy-associated complications in sickle cell disease and control.

Variable	HbSC	HbSS	HbAA	SS versus SC		SS versus AA		SC versus AA	
				χ^2	P-value	χ^2	P-value	χ^2	P-value
Total pregnancies (n)	66	98	160						
Gestational hypertension									
Pregnancy-induced hypertension	9	10	6	0.45	0.50	4.35	0.04	7.37	0.007
Pre-eclampsia	14	20	10	0.02	0.89	11.86	0.0005	11.02	0.001
Eclampsia	0	1	0	-	-	-	-	-	-
Haemorrhage									
Antepartum	3	3	2	0.25	0.62	1.05	0.31	2.35	0.13
Postpartum	5	7	6	0.01	0.92	1.46	0.23	1.48	0.22
Gestational diabetes	0	3	2	2.06	0.15	1.05	0.31	0.83	0.36
Retained placenta	0	1	0	-	-	-	-	-	-
Uneventful pregnancies	41	34	144	11.95	0.0005	86.89	<0.0001	22.61	<0.0001
Sickle cell-related complications									
Painful crises	10	29	0	4.54	0.03				
Acute chest syndrome	6	12	0	0.40	0.53				
Urinary tract infection	12	14	0	0.45	0.50				
Maternal death	0	0	0						

hypertension and pre-eclampsia. Women with haemoglobinopathies have higher incidence of pregnancy-induced hypertension and preeclampsia when compared with control. No SC and AA pregnancies manifested eclampsia compared with one SS. Maternal genotypes have no significant effect on other maternal complications. There was no difference on the incidence of sickle-related clinical events during pregnancy in SC mothers compared SS mothers. This study did not record any maternal death.

4. Discussion

The incidence of SCD in pregnancy varies significantly in different parts of the world. The incidence of SCD in pregnancy in this study was 6.9 per 1000 deliveries. This finding was similar to an incidence of 8.7 per 1000 deliveries in Benin, Nigeria [10]. This is higher than reported incidence of 0.95 per 1000 deliveries in Tanzania [11]. Nigeria has a high prevalence of SCD although population data is not available. Data about the incidence of pregnancies in women with SCD are mostly institutional.

It is well established that women with SCD are at increased risk of maternal and fetal complications during pregnancy when compared with healthy women [12] [13] [14] [15] [16]. Studies in low income countries have reported maternal mortality rate of 7% - 12% among women with SCD in pregnancy, reflecting limited services and inadequate antenatal care [13]. We report for the first time the outcome of pregnant women with SCD delivering at the Alex Ekwueme

Federal University Teaching Hospital Abakaliki and compare these outcomes with a comparison group of women with no hemoglobinopathies. Unlike other studies in developing countries, this study indicates that there is significant improvement in the outcome of women with SCD compared with women without hemoglobinopathies. The SCD mortality rate was 0% of all maternal mortality, which is different from what has been observed in other studies in Africa suggesting that advances in care for patients with SCD have led to improvement in the outcome for women with SCD in pregnancy although other maternal and perinatal outcomes were worse when compared with women with genotype AA.

Pregnancy has been shown to exacerbate sickle cell crises and increase the rate of hospitalization. Recent study indicates that sickle cell crisis occurred in over 50% of the pregnant women with SCD [14]. However, sickle cell crises were observed in 15% of women with HbSC and 30% of those with HbSS in this study, which is consistent with studies conducted in the United States and Ghana [15] [16]. Similarly, the incidence of sickle cell related complication such acute chest syndrome and urinary tract infection were commoner among pregnant women with HbSS when compared with those with HbSC.

The HbSS women were at a greater risk of being anemic when compared with those with HbSC. Anemia is one of the major complications of sickle cell disease and may be caused by hemolysis or trapping of the red blood cells in the spleen [16]. Anemia in pregnancy has been found to be associated with increased risk for preterm premature rupture of membranes, spontaneous preterm labor, preterm delivery, poor intrauterine growth, and low birth weight infants, which in turn results in higher perinatal morbidity and mortality, and a higher infant mortality rate [16].

The caesarean section was more likely to be performed for pregnant women with SCD than for the comparison group. The caesarean is likely to be elective more often in SCD because of fetal compromise and previous history. Closer fetal monitoring and a lower threshold for tolerating abnormal fetal heart rate patterns, may also contribute to this trend. The caesarean section may also be performed as a result of fetal distress, failure of labor to progress, or discretionary repeated need for surgery. However, because of the retrospective nature of this study, differences between elective and emergency caesarean section could not be established.

Overall, pregnancy outcome was worse in women with SCD when compared with those without haemoglobinopathy. However, the findings of this study suggest that pregnancy complications were less in SC disease than in SS disease. This finding was consistent with reports from several studies [1]-[16]. Gestational age at delivery, mode of delivery, live birth rate, and birthweight in SCD pregnancies showed significant difference to AA controls. The outcomes of pregnancy were worse among women with HbSS when compared with HbSC and HbAA. The better pregnancy outcome in women with HbSC is consistent with the behaviour of the SC genotype, which is often mild and may not be diagnosed

until later in adult life. Although HbSC women had better pregnancy outcome, this study shows that the incidence of sickle cell-related complications did not differ among women with genotype SS and SC. Therefore, it is not yet possible to predict those SC patients who will develop severe complications in pregnancy and it is a good practice to monitor all pregnancies in SCD closely with delivery in hospital.

5. Conclusion

In conclusion, this study showed that the maternal mortality in SS and SC patients in pregnancy is not different from those of HbAA women in our hospital, although other maternal and fetal outcomes were still poor when compared with women without SCD. Therefore, preconceptional care and adequate antenatal and postnatal management by a multidisciplinary team and establishment of sickle cell clinic for SCD in pregnancy will help to further improve pregnancy outcome among these women in our facility.

Limitations

This study has some limitations. Firstly, this is hospital-based study which includes only women that were managed in the hospital but many women deliver in rural areas without reaching health facility so community-based studies are a better tool. Secondly, due to lack of follow up after discharge, the data on neonatal morbidity and mortality as well as maternal outcome for the rest of the puerperium were not available for analysis and finally retrospective nature of study limits its validity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Olugbenga, A.O. (2018) Managing Sickle Cell Disease in Pregnancy, the Success and the Challenges: Our Experience in a Semi-Urban Tertiary Health-Care Facility, Southwest, Nigeria. *Tropical Journal of Obstetrics and Gynaecology*, **35**, 342-347. https://doi.org/10.4103/TJOG.TJOG_37_18

[2] Wilson, N.O., Ceesay, F.K., Hibbert, J.M., Driss, A., Obed, S.A., Adjei, A.A., *et al.* (2012) Pregnancy Outcomes among Patients with Sickle Cell Disease at Korle-Bu Teaching Hospital, Accra, Ghana: Retrospective Cohort Study. *The American Journal of Tropical Medicine and Hygiene*, **86**, 936-942. https://doi.org/10.4269/ajtmh.2012.11-0625

[3] Oteng-Ntim, E., Meeks, D., Seed, P.T., Webster, L., Howard, J., Doyle, P. and Chappell, L.C. (2015) Adverse Maternal and Perinatal Outcomes in Pregnant Women with Sickle Cell Disease: Systematic Review and Meta-Analysis. *Blood*, **125**, 3316-3325. https://doi.org/10.1182/blood-2014-11-607317

[4] Rezai, S., Cavallo, G., Gottimuk-Kala, S., Mercado, R. and Henderson, E.C. (2016) Dual Case Reports of Haemoglobin SC Disease in Pregnancy. *Obstetrics & Gyne-*

cology International Journal, **4**, Article ID: 00105.
https://doi.org/10.15406/ogij.2016.04.00105

[5] Elenga, N., Adeline, A., Balcaen, J., Vaz, T., Calvez, M., Terraz, A., *et al*. (2016) Pregnancy in Sickle Cell Disease Is a Very High-Risk Situation: An Observational Study. *Obstetrics and Gynecology International*, **2016**, Article ID: 9069054.
https://doi.org/10.1155/2016/9069054

[6] Odum, C.U., Anorlu, R.I., Dim, S.I. and Oyekan, T.O. (2002) Pregnancy Outcome in HbSS-Sickle Cell Disease in Lagos, Nigeria. *West African Journal of Medicine*, **21**, 19-23.

[7] Kuo, K., Aviram, A., Merril, E.M. and Caughey, B.A. (2016) Optimal Timing of Delivery for Women with Sickle Cell Disease. *American Journal of Obstetrics & Gynecology*, **214**, S272-S273. https://doi.org/10.1016/j.ajog.2015.10.542

[8] Omo-Aghoja, I.O. and Okonofua, F.E. (2007) Pregnancy Outcome in Women with Sickle Cell—A Five Year Review. *Nigerian Postgraduate Medical Journal*, **14**, 151-154.

[9] Rahimy, M.C., Gangbo, A., Adjou, R., Deguenon, C., Goussanou, S. and Alihonou, E. (2000) Effect of Active Prenatal Management on Pregnancy Outcome in Sickle Cell Disease in an African Setting. *Blood*, **96**, 1685-1689.

[10] Boafor, T.K., Olayemi, E., Galadanci, N., Hayfron-Benjamin, C., Dei-Adomakoh, Y., Segbefia, C., *et al*. (2016) Pregnancy Outcome in Women with Sickle-Cell Disease in Low and High Income Countries: A Systematic Review and Meta-Analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, **123**, 691-698.
https://doi.org/10.1111/1471-0528.13786

[11] Nwabuko, O.C., Okoh, D.A., Iyalla, C. and Omunakwe, H. (2016) Prevalence of Sickle Cell Disease among Pregnant Women in a Tertiary Health Center in South-South Nigeria. *Sub-Saharan African Journal of Medicine*, **3**, 132-136.
https://doi.org/10.4103/2384-5147.190843

[12] Ocheni, S., Onah, H.E., Ibegbulam, O.G. and Eze, M.I. (2007) Pregnancy Outcomes in Patients with Sickle Cell Disease in Enugu, Nigeria. *Nigerian Journal of Medicine*, **16**, 227-230.

[13] Ugboma, H.A. and George, I.O. (2015) Sickle Cell Disease in Pregnancy: Maternal and Fetal Outcome in Port Harcourt, Nigeria. *British Journal of Medicine and Medical Research*, **7**, 40-44. https://doi.org/10.9734/BJMMR/2015/11602

[14] Grosse, S.D., Odame, I., Atrash, H.K., Amendah, D.D., Piel, F.B. and Williams, T.N. (2011) Sickle Cell Disease in Africa: A Neglected Cause of Early Childhood Mortality. *American Journal of Preventive Medicine*, **41**, S398-S405.
https://doi.org/10.1016/j.amepre.2011.09.013

[15] Graham, R.S., Luana, L.L., Mark, C., Ian, R.B. and Minerva, T. (2004) Outcome of Pregnancy in Homozygous Sickle Cell Disease. *Obstetrics & Gynecology*, **103**, 1278-1285.
https://doi.org/10.1097/01.AOG.0000127433.23611.54

[16] Njamen, T.N., Tolefack, P.N., Ngouadjeu, E., Nguefack, C.T.C. and Nana, C.N. (2018) Pregnancy Outcome among Patients with Homozygous Sickle Cell Disease: Eight Years Retrospective Cohort in a Tertiary Hospital in Sub-Saharan Africa. *Archives of Gynecology and Obstetrics*, **1**, 4-9.

International Journal of Clinical Medicine, 2019, 10, 404-412
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

The Relevance of Serum Cystatin C Level of Different Classification of Atrial Fibrillation

Yuqing Duan, Jianhui Xu, Wei Hu, Peng Li, Rui Li*

Department of Cardiology, The Central Hospital of Xiaogan, Wuhan University of Science and Technology, Wuhan, China
Email: dyqqh7@126.com, *chinaxglr@126.com

How to cite this paper: Duan, Y.Q., Xu, J.H., Hu, W., Li, P. and Li, R. (2019) The Relevance of Serum Cystatin C Level of Different Classification of Atrial Fibrillation. *International Journal of Clinical Medicine*, **10**, 404-412.
https://doi.org/10.4236/ijcm.2019.108033

Received: July 16, 2019
Accepted: August 13, 2019
Published: August 16, 2019

Abstract

Objective: To investigate the relationship between serum level of cystatin C (Cys-C) and AF (atrial fibrillation) and its clinical classification. **Method:** From January 2017 to April 2019, 168 cases of Xiaogan Central Hospital were chosen as the object of this study. The subjects were divided into 86 patients with AF and 82 patients in the control group. The AF group was divided into paroxysmal AF group (29 cases), persistent AF group (27 cases) and permanent AF group (29 cases) according to the European atrial fibrillation management guidelines and the North America Society of Pacing and Electrophysiology (NASPE) arrhythmia group organized the categorization of AF. **Results:** Compared with the control group, the level of the serum Cys-C was significantly higher in the AF group, the difference was statistically significant ($P < 0.05$). There was significant difference in Cys-C level in patients with different types of AF ($P < 0.05$). The levels of neutrophil percentage, low density lipoprotein cholesterol (LDL-C), left ventricular diameter, left atrial diameter, C-reactive protein (CRP) and homocysteine in the AF group were significantly higher than those in the control group ($P < 0.05$). The difference of neutrophil percentage, LDL-C, left ventricular ejection fraction, left atrial diameter, CRP and homocysteine levels in patients with different types of atrial fibrillation was statistically significant ($P < 0.05$). Logistic analysis showed that the serum Cys-C level, CRP, homocysteine, left ventricular diameter, left atrial diameter could be used as an independent predictor of atrial fibrillation when other factors were corrected. **Conclusion:** Serum Cys-C level in atrial fibrillation group is significantly higher than the control group, there are differences between different atrial fibrillation clinical classification, its level increased with duration of atrial fibrillation. Serum Cys-C level and inflammatory markers CRP, WBC and neutrophilic granulocyte percentage were positively correlated, indicating that serum cystatin C is associated with chronic inflammation, involved in the occurrence of atrial fibrillation, maintain and recurrence. Logistic analysis showed that the serum cystatin C level could be

used as an independent predictor of atrial fibrillation when other factors were corrected.

Keywords

Cystatin C, Atrial Fibrillation, Inflammatory

1. Introduction

Atrial fibrillation (AF) is a complex and dangerous arrhythmia. Serious disorder of atrial electrical activity, which is a regular and orderly electrical activity and replaced by rapid and disordered tremor, is the main cause of its occurrence. Epidemiological investigation shows that the prevalence of AF in Chinese is about 0.77% - 2.8%, accounting for about one-third of all hospitalized arrhythmia patients. The morbidity and prevalence of atrial fibrillation increased with age [1]. The main causes of death in patients with atrial fibrillation are progressive heart failure (HF), cardiac arrest and cerebral apoplexy [2]. Reasonable treatment in time can significantly reduce mortality in patients with atrial fibrillation. Therefore, how to diagnose atrial fibrillation as soon as possible and assess the patient's condition, so that these patients get treatment as soon as possible, to minimize the damage and harm caused by the disease, is still a hot topic in the medical field. Cystatin C (Cys-C) is a low-molecular-weight secretory protein of the human body. Almost all nucleated cells can produce this secreted protein, and the secretion process is rarely affected by factors such as gender, age, bilirubin, blood lipids, muscle mass, etc., so the serum Cys-C production rate and serum level are relatively constant. In recent years, it has been found that serum Cys-C is more sensitive than creatinine (Cr) and Serum urinary nitrogen (BUN) as an indicator of glomerular filtration rate. It is currently used as a sensitive indicator for assessing early damage to renal function [3] [4]. In 2010, Deo *et al*. showed that serum Cys-C level was positively correlated with the prevalence of atrial fibrillation. It was concluded that renal dysfunction, which was evaluated by serum Cys-C, was an independent predictor of AF prevalence [5]. In recent years, Cys C has been found to be able to predict new or worsening cardiovascular diseases [6]. In addition, studies have shown that higher levels of serum Cys-C may increase the risk of cardiovascular autonomic nervous dysfunction [7]. At present, many literatures and experiments have proved that elevated serum Cys-C is an independent risk factor for atrial fibrillation [8]. However, whether there is a correlation between serum Cys-C level and types of atrial fibrillation still needs to be further explored. The purpose of this study was to explore the relationship between cystatin C and atrial fibrillation types, and to provide a new idea for early clinical evaluation of atrial fibrillation types.

2. Date and Methods

1) Clinical Data: 86 patients with non-valvular atrial fibrillation who were

admitted to Xiaogan Central Hospital from January 2017 to April 2019. According to the European Society of Cardiovascular Disease (ESC), the North American Pacing and Electrophysiology Society (NASPE), the above atrial fibrillation patients were divided into three subgroups, paroxysmal AF (29 cases). People, accounting for 33.72%; persistent AF (27 cases), accounting for 31.39%; permanent AF (30 cases), accounting for 34.88%. At the same time, 82 patients in the normal control group were selected, and the general situation (gender, age, creatinine, cystatin-C, etc.) matched the atrial fibrillation group and the electrocardiogram was normal sinus rhythm. Inclusion criteria: Atrial fibrillation can be diagnosed according to the surface electrocardiogram (ECG) or 24-hour Holter, the patients' ages were 18 - 99 years, male or female. Exclusion criteria: patients with congenital heart disease, rheumatic heart disease, and prosthetic valve replacement or repair; history of coronary artery bypass grafting or coronary stent implantation; acute coronary syndrome (ACS) within 3 months of onset; patients with clear hypertension, diabetes, blood disease, thyroid dysfunction, liver and kidney dysfunction, autoimmune diseases, tumor diseases, nervous system diseases; patients with acute and chronic infectious diseases; patients with trauma, surgical history and anti-infective drugs in the recent 30 days; New York Heart Association Cardiac Function Grade 3 or more; patients with statins lipid-lowering drugs in the recent 30 days.

2) Methods Record: The patient's general information, gender, age, atrial fibrillation type, CHA2DS2VASc score, HAS-BLED score, the peripheral venous blood was collected on an empty stomach the next morning, blood routine, liver function, renal function, electrolytes, blood lipids, blood homocysteine, high-sensitivity C-reactive protein, etc. Early cardiac color Doppler ultrasound examination, measurement of left atrial diameter (LAD), left ventricular end-diastolic diameter (LVDD), left ventricular ejection fraction (LVEF).

3) Statistical Analysis: Statistical analysis was carried out by SPSS 23.0 software. The comparison between the two groups of measurement data subject to normal distribution was carried out by T-test; the comparison of more than three groups was carried out by one-way ANOVA test, and the comparison between groups was carried out by T-test. The measurement data not subject to normal distribution was carried out by Wilcoxon rank sum test of two independent samples; and the counting data was analyzed by χ^2 test. For comparison of multi-group measurement data, variance analysis was used for normal distribution and homogeneous variance, Kruskal-Wallis H test was used for non-normal distribution or uneven variance. Logistic regression analysis was used to analyze the risk factors of atrial fibrillation ($P < 0.05$).

3. Results

3.1. Comparison of Clinical Data between Atrial Fibrillation Group and Control Group

The general information of the patients in the two groups is shown in Table 1.

Table 1. Comparison of clinical data between atrial fibrillation group and control group.

Related indicators	Control group (n = 82)	AF group (n = 86)	Statistics	*P*
age	69.55 ± 10.19	71.40 ± 11.21	t = 1.901	*P* = 0.063
WBC count (10^9/l)	6.29 ± 3.56	6.31 ± 2.48	t = 0.109	*P* = 0.929
Neutrophil percentage (%)	64.25 ± 8.92	69.33 ± 9.03	t = 3.271	**P = 0.002**
Creatinine (mmoI/L)	84.52 ± 10.23	82.33 ± 11.96	t = 1.505	*P* = 0.139
Total cholesterol (mmol/L)	3.48 ± 1.01	3.53 ± 0.91	t = 1.033	*P* = 0.501
LDL-C (mmol/L)	1.23 ± 0.55	1.66 ± 0.62	t = 2.880	**P = 0.006**
HDL-C (mmol/L)	1.16 ± 0.54	1.18 ± 0.29	t = 0.647	*P* = 0.224
Triglyceride (mmol/L)	1.32 ± 0.56	1.28 ± 0.83	t = 0.561	*P* = 0.576
LVEF (%)	60.22 ± 7.48	53.93 ± 8.14	t = 2.133	**P = 0.004**
Left inner diameter (cm)	4.02 ± 1.23	4.70 ± 0.66	t = 2.544	**P = 0.014**
Left atrial diameter (cm)	3.14 ± 1.18	4.34 ± 0.77	t = 2.976	**P < 0.001**
CRP (mg/L)	2.05 ± 10.98	6.93 ± 17.76	t = 2.23	**P = 0.004**
Homocysteine (mmol/L)	7.96 ± 5.21	13.96 ± 3.40	t = 3.79	**P < 0.001**
Cystatin C (mg/L)	0.67 ± 0.98	0.92 ± 0.39	t = 4.150	**P < 0.001**

WBC count = White blood cell count; LDL-C = Low density lipoprotein cholesterol; HDL-C = High density lipoprotein cholesterol; LVEF Left ventricular ejection fraction.

Compared with the control group, the average age of the control group was 69.55 ± 10.19 years, and that of the atrial fibrillation group was 71.40 ± 11.21 years. The percentage of neutrophils, LDL-C, left ventricular diameter, left atrial diameter, CRP, HCY and serum Cys-C levels in the atrial fibrillation group were higher than the control group, the difference was statistically significant ($P < 0.05$). The left ventricular ejection fraction of the atrial fibrillation group was smaller than that of the control group, and the difference was statistically significant ($P < 0.05$). There was no significant difference in white blood cell count, creatinine, total cholesterol, high density lipoprotein cholesterol and triglyceride between the two groups ($P > 0.05$).

3.2. Comparison of Clinical Data between Different Atrial Fibrillation Groups

The average age of patients with paroxysmal atrial fibrillation was 67.45 ± 12.25, the average age of patients with persistent atrial fibrillation was 66.92 ± 9.88 years, and the average age of patients with permanent atrial fibrillation was 76.67 ± 9.15 years old. There was no significant difference in the age of patients with different types of atrial fibrillation (F = 5.018, $P = 0.212$). The serum Cys-C levels in the permanent AF were higher than in the persistent AF, and the persistent AF was higher than the paroxysmal AF. All were statistically significant ($P < 0.05$). At the same time, the study found that the difference in the percentage of neutrophils, LDL-C, left atrial diameter, LVEF, CRP, HCY in different types of patients were statistically significant ($P < 0.05$), of which, for neutrophils Per-

centage, LDL-C, left atrial diameter, CRP, HCY, permanent AF were higher than paroxysmal AF and persistent AF, the difference was statistically significant ($P < 0.05$). For left ventricular ejection fraction, the permanent AF was lower than paroxysmal AF and persistent AF, the difference was statistically significant ($P < 0.05$). There were no significant differences in white blood cell count, creatinine, total cholesterol, high-density lipoprotein cholesterol, and triglycerides between patients with different types of atrial fibrillation ($P > 0.05$) (Table 2).

3.3. Logistic Multivariate Analysis

As shown in Table 3, univariate logistic regression analysis was performed on factors such as age, neutrophil percentage, LDL-C, plasma homocysteine, CRP, and serum Cys-C, and then multivariate analysis was performed on single-factor meaningful variables. It is shown that serum Cys-C, CRP, homocysteine, cystatin C, left ventricular diameter, and left atrial diameter are risk factors for atrial fibrillation.

4. Discussion

Atrial fibrillation is a disease that increases mortality. Some studies have shown that atrial fibrillation can increase the risk of sudden cardiac death, major cardiovascular adverse events, heart failure, ischemic heart disease, cerebral infarction, peripheral artery disease, chronic kidney disease and other related diseases [9]. Current studies suggest that atrial fibrillation is mainly associated with atrial remodeling, electrical remodeling, autonomic nervous system function, gene mutation, increased activity of renin-angiotensin-aldosterone system and

Table 2. Comparison of clinical data between different atrial fibrillation groups.

Related indicators	Paroxysmal AF (n = 29)	Persistent AF (n = 27)	Permanent AF (n = 30)	Statistics	*P*
Age	67.45 ± 12.25	66.92 ± 9.88	76.67 ± 9.15	F = 5.018	$P = 0.212$
WBC count (10^9/l)	6.03 ± 1.71	6.98 ± 3.29	7.01 ± 2.22	F = 0.668	$P = 0.518$
Neutrophil percentage (%)	68.45 ± 9.66	70.71 ± 10.44	74.88 ± 7.91	H = 10.033	**$P = 0.004$**
Creatinine (mmoI/L)	77.77 ± 10.93	80.9 ± 9.47	82.15 ± 13.45	H = 2.838	$P = 0.242$
Total cholesterol (mmol/L)	3.67 ± 0.83	3.85 ± 0.95	3.21 ± 0.87	F = 2.092	$P = 0.137$
LDL-C (mmol/L)	1.52 ± 0.48	1.88 ± 0.67	2.01 ± 0.66	F = 8.230	**$P = 0.003$**
HDL-C (mmol/L)	1.25 ± 0.27	1.26 ± 0.28	1.07 ± 0.30	F = 2.098	$P = 0.136$
Triglyceride (mmol/L)	1.59 ± 1.25	1.25 ± 0.72	1.10 ± 0.54	F = 1.198	$P = 0.313$
LVEF (%)	57.45 ± 3.64	55.85 ± 8.35	51.29 ± 0.95	F = 7.555	**$P = 0.004$**
Left inner diameter (cm)	4.51 ± 0.58	4.68 ± 0.75	4.84 ± 0.64	F = 0.845	$P = 0.437$
Left atrial diameter (cm)	3.82 ± 0.77	4.42 ± 0.71	4.61 ± 0.68	F = 10.265	**$P = 0.001$**
CRP (mg/L)	1.16 ± 1.98	2.02 ± 1.05	14 ± 25.1	H = 26.236	**$P = 0.001$**
Homocysteine (mmol/L)	16.7 ± 3.81	17.3 ± 1.93	21.22 ± 3.79	F = 15.912	**$P < 0.001$**
Cystatin C (mg/L)	0.65 ± 0.09	0.82 ± 0.27	1.15 ± 0.45	H = 34.332	**$P < 0.001$**

Table 3. Logistic multivariate analysis results.

Influencing factor	B	S.E.	Wald	*P*-value	OR	95% CI
Cystatin c	2.668	0.256	7.986	0.004	12.56	0.132 - 49.895
Neutrophil percentage	1.180	2.75	0.768	0.108	2.75	0.654 - 10.411
LDL-C	0.120	0.346	0.059	0.988	1.601	1.447 - 1.768
CRP	0.125	0.028	18.186	0.000	1.522	1.144 - 1.965
Homocysteine	0.134	0.036	15.981	0.000	1.301	1.159 - 1.464
LVEF	−0.049	0.038	0.965	0.213	0.951	0.793 - 1.128
Left inner diameter	0.137	0.044	6.175	0.010	1.215	1.052 - 1.317
Left atrial diameter	0.104	0.022	12.358	0.001	1.098	1.051 - 1.181

inflammatory reaction [10]. Inflammatory reaction was found to be closely related to the occurrence and progression of atrial fibrillation. Inflammatory factors such as interleukin (IL) [11], C-reactive protein (CRP) [12], tumor necrosis factor-α (TNF-α) [13] were found to be associated with atrial fibrillation. Cysteine protease inhibitor C (Cys-C) is a low molecular weight (13 kDa) protein produced by all nucleated cells. More and more studies have confirmed that Cys-C may play a key role in the detection and evaluation of cardiovascular diseases in addition to being an indicator of impaired renal function. Wang *et al*. have shown that higher levels of serum Cys-C are independently associated with increased risk of cardiovascular events, and this risk is not significantly associated with GFR [14]. Cys C is also released from cardiac myocytes, and hypoxia increases its production [15]. Increased serum Cys-C level can inhibit the effect of protease and lead to remodeling of vascular wall. At the same time, Cys-C can reduce the decomposition of atrial fibroblasts and cause myocardial fibrosis. Myocardial fibrosis is the pathological basis of the occurrence and progression of atrial fibrillation [16]. HCY is an independent predictor of cardiovascular and cerebrovascular diseases [17]. Serum Cys-C can inhibit the activity of cysteine protease and reduce the decomposition of HCY, damage vascular endothelium and inhibit the synthesis of NO. Both of them participate in the oxidative stress process, lead to ischemia and hypoxia, and cause changes in atrial structure. It is easy to induce atrial fibrillation [18]. Cys-C is involved in many inflammatory reactions. Serum Cys-C and its degradation products can directly affect the migration, chemotaxis and phagocytosis of neutrophils, thus participating in the whole inflammatory process [19]. Inflammatory reaction leads to fibrosis of atrial myocytes, which leads to atrial enlargement, and finally changes of atrial structure, leading to atrial fibrillation. Korantzopoulos *et al*. found that inflammation contributes to electrical remodeling of atrial fibrillation, especially in the recurrence or evolution of atrial fibrillation into permanent atrial fibrillation [20], which is consistent with the results of Samouilidou's study [21]. In Buddha's Framingham's study [22], we found a close correlation between LAD and

atrial fibrillation: the prevalence of atrial fibrillation increased with the increase of LAD. Wang Xin and other studies indicated that high serum Cys-C level was a risk factor for left atrial dilatation [23], and electrical remodeling caused by atrial dilatation and fibrosis could trigger atrial fibrillation [24]. High Cys-C level is a highly sensitive marker of mild renal insufficiency. Mild renal insufficiency is associated with microvascular endothelial insufficiency [25]. High Cys-C level may lead to microvascular endothelial insufficiency, activate RAAS system, accumulate extracellular matrix, accelerate atrial fibrosis, and activation of RAAS system may also lead to renal function damaged.

In this study, we found that serum Cys-C level in AF group was significantly higher than that in non-AF group. There were differences among clinical types of AF. The level of Cys-C increased with the duration of AF ($P < 0.05$). In the process of analyzing the correlation between Cys-C and various clinical indicators, we found that serum Cys-C and inflammation were associated with AF. Indicators such as hypersensitivity protein, white blood cell count and percentage of neutrophils were positively correlated, which supported that the occurrence and development of atrial fibrillation was closely related to inflammation. At the same time, the level of LDL-C in atrial fibrillation group was higher than that in non-atrial fibrillation group, and increased with the prolongation of atrial fibrillation time ($P < 0.05$). In multivariate logistic regression analysis, we found that left ventricular diameter can be a risk factor for atrial fibrillation. This may be because atrial fibrillation can lead to ventricular fibrosis, enlargement of ventricular diameter, decrease of left ventricular ejection fraction, and decrease of left ventricular ejection fraction, which can also promote atrial enlargement. They form a vicious circle. Logistic analysis showed that the elevated serum cystatin C level could be used as an independent predictor of atrial fibrillation after adjusting for other factors.

Because the measurement of serum Cys-C is simple, inexpensive and painful, and it can also be used as an evaluation index of renal function, serum Cys-C is expected to be an effective marker for evaluating the occurrence, maintenance and recurrence of atrial fibrillation, and has important clinical significance. Serum Cys-C is also an index closely related to renal function, which is of great significance for research. It is also important to investigate and analyze the relationship between kidney disease and cardiovascular disease. However, this study is a retrospective analysis. Although many factors that may affect the results of the study have been excluded, due to the small sample size and the drug (the patient may take long-term medications such as statins and other cardiovascular diseases before admission) and various factors, the persuasiveness of the research results is limited, and the reliability of the final conclusion still needs to be further confirmed by large-scale and more rigorous experimental analysis. The influence of many factors, the persuasiveness of the research results is limited, and the reliability of the final conclusion still needs to be further confirmed by large-scale and more rigorous experimental analysis.

Conflicts of Interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] Chugh, S.S., Havmoeller, R., Narayanan, K., *et al*. (2014) Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. *Circulation*, **129**, 837-847. https://doi.org/10.1161/CIRCULATIONAHA.113.005119

[2] Kirchhof, P., Benussi, S., Kotecha, D., *et al*. (2016) ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration with EACTS. *European Heart Journal*, **37**, 2893-2962. https://doi.org/10.1093/eurheartj/ehw210

[3] Ferguson, T.W., Komenda, P. and Tangri, N. (2015) Cystatin C as a Biomarker for Estimating Glomerular Filtration Rate. *Current Opinion in Nephrology and Hypertension*, **24**, 295-300. https://doi.org/10.1097/MNH.0000000000000115

[4] Inker, L.A., Schmid, C.H., Tighiouart, H., *et al*. (2012) Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *New England Journal of Medicine*, **367**, 20-29. https://doi.org/10.1056/NEJMoa1114248

[5] Deo, R., Katz, R., Kestenbaum, B., *et al*. (2010) Impaired Kidney Function and Atrial Fibrillation in Elderly Subjects. *Journal of Cardiac Failure*, **16**, 55-60. https://doi.org/10.1016/j.cardfail.2009.07.002

[6] Guerchicoff, A., Stone, G.W., Mehran, R., *et al*. (2015) Analysis of Biomarkers for Risk of Acute Kidney Injury after Primary Angioplasty for Acute ST-Segment Elevation Myocardial Infarction: Results of the HORIZONS-AMI Trial. *Catheterization Cardiovascular Intervention*, **585**, 335-342. https://doi.org/10.1002/ccd.25620

[7] Yang, X., Lin, Q., Li, X., Wu, L., Xu, W., Zhu, Y., Yao, B., *et al*. (2019) Cystatin C Is an Important Biomarker for Cardiovascular Autonomic Dysfunction in Chinese Type 2 Diabetic Patients. *Journal of Diabetes Research*, **2019**, Article ID: 1706964. https://doi.org/10.1155/2019/1706964

[8] Peng, L. and Fang, Z. (2015) Expression and Significance of Serum Heat Shock Protein 70 and Cystatin C in Elderly Patients with Chronic Atrial Fibrillation. *Hebei Medical College*, No. 9, 1455-1458.

[9] Khaji, A., Kowey, P.R., *et al*. (2016) Update on Atrial Fibrillation. *Texas Heart Institute Journal*, **43**, 412-414. https://doi.org/10.14503/THIJ-16-5916

[10] Huang, C., Zhang, S., Huang, D., *et al*. (2018) Atrial Fibrillation: Current Understanding and Treatment Recommendations-2018. *Chinese Journal of Cardiac Pacing and Electrophysiology*, **32**, 315-368.

[11] Marcus, G.M., Smith, L.M., Ordovas, K., *et al*. (2010) Intracardiac and Extracardiac Markers of Inflammation during Atrial Fibrillation. *Heart Rhythm*, **7**, 149-154. https://doi.org/10.1016/j.hrthm.2009.10.004

[12] Psychari, S.N., Apostolou, T.S., Sinos, L., *et al*. (2005) Relation of Elevated C-Reactive Protein and Interleukin-6 Levels to Left Atrial Size and Duration of Episodes in Patients with Atrial Fibrillation. *American Journal of Cardiology*, **95**, 764-767. https://doi.org/10.1016/j.amjcard.2004.11.032

[13] Qu, Y.C., Du, Y.M., Wu, S.L., *et al*. (2009) Activated Nuclear Factor-kappaB and Increased Tumor Necrosis Factor-Alpha in Atrial Tissue of Atrial Fibrillation. *Scandinavian Cardiovascular Journal*, **43**, 292-297. https://doi.org/10.1080/14017430802651803

[14] Wang, J., Sim, A.S., Wang, X.L., *et al*. (2008) Relations between Markers of Renal Function, Coronary Risk Factors and the Occurrence and Severity of Coronary Artery Disease. *Atherosclerosis*, **197**, 853-859. https://doi.org/10.1016/j.atherosclerosis.2007.07.034

[15] Akgul, O., *et al*. (2013) Predictive Value of Elevated Cystatin C in Patients Undergoing Primary Angioplasty for ST-Elevation Myocardial Infarction. *Journal of Critical Care*, **28**, 13-20. https://doi.org/10.1016/j.jcrc.2013.03.004

[16] Inker, L.A., Schmid, C.H., Tighiouart, H., *et al*. (2012) Estimating Glomerular Filtration Rate from Scrum Creatinine and Cystatin C. *New England Journal of Medicine*, **367**, 20-29. https://doi.org/10.1056/NEJMoa1114248

[17] Chen, T., Chen, Y., Wang, Y., *et al*. (2013) Clinical Application of Plasma Cystatin C, Homocysteine, D-Dimer and Hypersensitive C-Reactive Protein in the Diagnosis and Treatment of Acute Cerebral Infarction. *International Journal of Laboratory Medicine*, No. 23, 3168-3169+3171.

[18] Zhang, R. (2014) Analysis of Correlation between Plasma Cystatin C and Homocysteine Levels and Carotid Atherosclerosis in Patients with Acute Cerebral Infarction. *Journal of Practical Cardiocerebral Pulmonary Vascular Disease*, No. 10, 28-30.

[19] Bengtsson, E., To, F., Grubb, A., *et al*. (2005) Absence of the Protease Inhibitor Cystatin C in Inflammatory Cells Results in Larger Plaque Area in Plaque Regression of apoE-Deficient Mice. *Atherosclerosis*, **180**, 45-53. https://doi.org/10.1016/j.atherosclerosis.2004.12.025

[20] Korantzopoulos, P., Kolettis, T., Siogas, K., *et al*. (2003) Atrial Fibrination and Electrical Remodeling I the Potential Role of Inflammation and Oxidative Stress. *Medical Science Monitor*, **9**, 226-229.

[21] Samouilidou, E.C. and Grapsa, E. (2008) Relationship of Serum Cystatin C with C-Reactive Protein and Apolipoprotein A1 in Patients on Hemodialysis. *Renal Failure*, **30**, 711-715. https://doi.org/10.1080/08860220802212973

[22] Pearce, E.N., Yang, Q., Benjamin, E.J., *et al*. (2010) Thyroid Function and Left Ventricular Structure and Function in the Framingham Heart Study. *Thyriod*, **20**, 369-373. https://doi.org/10.1089/thy.2009.0272

[23] Wang, X. (2012) Study on the Relationship between Serum Levels of Cystatin C and β-2 Microglobulin and Left Ventricular Structure and Function in Patients with Coronary Heart Disease. Shandong University, Jinan.

[24] Miller, L.M., Sood, M.M., Sood, A.R., *et al*. (2010) Cardiovascular Disease in End-Stage Renal Disease: The Challenge of Assessing and Managing Cardiac Disease in Dialysis Patients. *International Urology and Nephrology*, **42**, 1007-1014. https://doi.org/10.1007/s11255-010-9857-x

[25] Alhusseiny, A.H., Al-Nimer, M.S. and Al-Neamy, S.I. (2015) Assessment of Serum Cystatin C Levels in Newly Diagnosed Acute Myocardial Infarction at the Onset and at the Time of Hospital Discharge. *Cardiology Research*, **6**, 226-231. https://doi.org/10.14740/cr377w

International Journal of Clinical Medicine, 2019, 10, 413-420
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Septic Superficial Femoral Vein Thrombophlebitis Causing Pulmonary Emboli and Respiratory Failure: Case Report and Review of the Literature

Ziad Fayad[1], Paul Guentert[2], Erin Rissler[2], Nuha Zackariya[2], Shivani Patel[2], Ali Sualeh[2], Mahmoud Al-Fadhl[2], Sufyan Zackariya[2], Grant Wiarda[2], Mallory Martin[3], Joseph Lake[4], Sarah Philbrick[2], Mark Walsh[2,4]

[1]General and Vascular Surgery, X-Ray Consultants, South Bend, IN, USA
[2]Saint Joseph Regional Medical Center, Mishawaka, IN, USA
[3]St. Luc Family Hospital, Tabarre, Haiti
[4]Indiana University School of Medicine, South Bend Campus, South Bend, IN, USA
Email: markwalshmd@gmail.com

How to cite this paper: Fayad, Z., Guentert, P., Rissler, E., Zackariya, N., Patel, S., Sualeh, A., Al-Fadhl, M., Zackariya, S., Wiarda, G., Martin, M., Lake, J., Philbrick, S. and Walsh, M. (2019) Septic Superficial Femoral Vein Thrombophlebitis Causing Pulmonary Emboli and Respiratory Failure: Case Report and Review of the Literature. *International Journal of Clinical Medicine*, **10**, 413-420.
https://doi.org/10.4236/ijcm.2019.108034

Received: July 18, 2019
Accepted: August 17, 2019
Published: August 20, 2019

Abstract

Septic pulmonary emboli rarely cause respiratory failure that requires mechanical ventilation. The most common causes of septic pulmonary emboli are related to intravenous drug abuse, indwelling intravenous catheters, endocarditis and septic pelvic thrombophlebitis. In addition, soft tissue injury-related thrombophlebitis rarely causes septic pulmonary emboli. We describe a unique case of a 43-year-old man who developed septic thrombophlebitis of the femoral vein following soft tissue injury from trauma to the shin with ensuing septic pulmonary emboli which necessitated endotracheal intubation and mechanical ventilation. The patient required mechanical ventilation for eleven days, developed empyema and grew out methicillin-resistant *Staphylococcus aureus* on blood cultures. A transesophageal echocardiogram was normal, and there was no indication of bacterial endocarditis. In addition to eleven days of mechanical ventilation, the patient was treated with intravenous heparin, cefepime and clindamycin. These medications were then discontinued and the patient was treated with weight-adjusted vancomycin. Following the return of cultures, the patient was treated for six weeks with ceftaroline 600 mg IV twice a day. In addition, the patient received bilateral thoracentesis followed by chest tube drainage until resolution of the pleural effusions. The patient made a complete recovery. We describe this case and the implications for differential diagnosis and treatment of these two uncommon conditions.

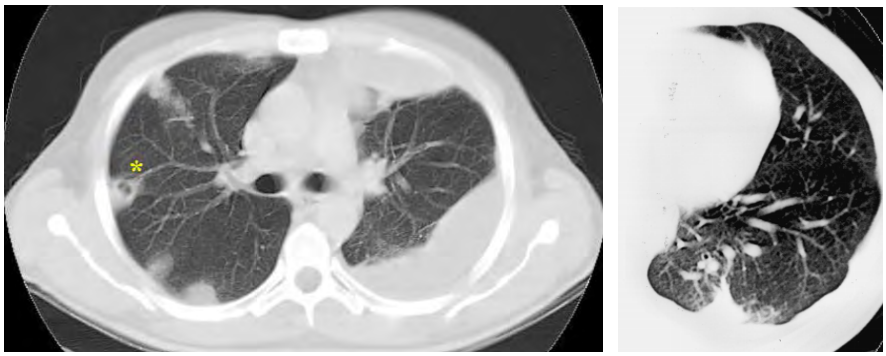
Keywords

Septic Thrombophlebitis, Pulmonary Emboli, Respiratory Failure, Critical Care

1. Introduction

Septic pulmonary embolism (SPE) is a variant of nonthrombotic pulmonary embolism in which a thrombus containing microorganisms causes an inflammatory reaction [1]. These thrombi can cause infarction and metastatic abscesses. SPE is a rare but serious condition that can pose as a difficult diagnostic challenge due to its nonspecific clinical and radiographic features, often leading to delayed diagnosis [2]. SPE has been associated with Lemierre's syndrome and periodontal disease [3] [4]. CT findings of SPE include peripheral nodules with or without cavitation, a feeding vessel sign, and wedge shaped peripheral lesions abutting the pleura (**Figure 1**) [2] [5] [6] [7]. Diagnosis of SPE is based on the presence of these CT findings and clinical evidence of infection [2].

In a systematic review of SPE from 1978 to 2012, the most common causative organism was *Staphylococcus aureus*, being responsible for 85% of cases [8]. This review of SPE found that most cases are associated with the use of intravenous drugs (26%), the use of an indwelling catheter (13%), or the presence of infectious endocarditis (12%). Less common causes include those associated with soft tissue infections (6%). The article cited three papers, documenting five patients in total with SPE originating from septic thrombophlebitis (ST) of the femoral vein. Of these five cases, three were associated with intravenous drug abuse, one case was associated with pyomyositis, and one was associated with a soft tissue infection following trauma to the great toe [9] [10] [11]. A recent case study also described, the papers cited above were referred to in past tense a case of SPE caused by an infected central venous port [12]. Search of the literature available on PubMed since 2012 shows no additional instances of SPE due to femoral vein thrombophlebitis. A search of the literature has also shown that SPE is



(a) (b)

Figure 1. CT findings seen in SPE. (a) Multiple peripheral nodules, and a feeding vessel sign (Asterix); (b) Wedge shaped peripheral lesion abutting the pleura [7].

rarely associated with respiratory failure [8]. We report a case of a man with SPE due to femoral vein thrombophlebitis that is not associated with intravenous drug use.

2. Case Description

A 43-year-old man presented to the emergency department with sudden onset malaise accompanied by swelling and pain in the right leg. Four days prior to admission, he hit his right shin on a trailer hitch in his garage causing bruising but no bleeding. The following day after returning home from work, he noticed a new onset rash on the right leg and acute onset malaise. Over the next two days, the patient slept the majority of the time, before seeking medical care. He has a history of underlying bilateral leg edema that began in 2015 following a right total hip arthroplasty, according to the patients report. He admitted to marijuana usage but denied any intravenous drug use. Written consent was given by the patient for publication of this case report.

On presentation, his vitals were: temperature of 102˚F, heart rate of 65, respiratory rate of 16, blood pressure of 117/86, and oxygen saturation of 98% on room air. He had bilaterally swollen lower extremities, more prominent on the right, with a large area of erythema and multiple bullae over the lateral right thigh and knee. The right mid-thigh was exquisitely tender to palpation but without crepitus. Right dorsalis pedis pulse was diminished and capillary refill was delayed. Breath sounds were decreased bilaterally and no murmurs were present. Over the next five hours, his vitals decompensated to a temperature of 102˚F, heart rate of 152, respiratory rate of 42, blood pressure of 102/73 and oxygen saturation of 92% on room air.

Initial labs demonstrated thrombocytopenia (105,000 platelets/μL), hyponatremia, a lactic acid level of 4.5, and an erythrocyte sedimentation rate of 38 mm/hr. However, there was no indication of leukocytosis. Blood, sputum, wound, and urine cultures were obtained. CT of the right lower extremity demonstrated edema, no gas, and a non-occlusive deep vein thrombosis of the right femoral vein; CT angiography of the chest demonstrated small filling defects of the right upper lobe segmental pulmonary artery as well as extensive abnormal lung nodularity of mixed solid and semisolid appearance (**Figure 1**). Transthoracic and transesophageal echocardiograms showed no valvular abnormalities.

He was initially placed on vancomycin, cefepime, and clindamycin and was intubated due to hypoxemic respiratory failure. Heparin drip was held until the first day of hospitalization when an MRI could be obtained to rule out brain emboli (no head CT with contrast at the time of admission was obtained since the patient had underlying chronic kidney disease and had already received contrast for lower extremity and chest CT). The MRI of the head showed no arterial occlusion, allowing heparin to be started. After being placed on antibiotics, he became afebrile on his first day of hospitalization. Blood, wound, and sputum cultures were positive for methicillin-resistant *S. aureus* (MRSA) and urine culture was positive for multiple gram-positive flora; therefore, cefepime and clindamycin were discontinued and the patient was treated with weight-adjusted van-

comycin which was given with a bolus dose of 30 mg/kg followed by a daily dose of 15 mg/kg that provided therapeutic levels.

The patient developed new onset leukocytosis which peaked at 16,910/μL on the sixth day of hospitalization. On the seventh day of hospitalization, the patient required bilateral chest tube placement for pleural effusions and to rule out and subsequently treat empyema. Additionally, ceftaroline 600 mg every 12 hours was added to his medication regimen. His leukocytosis resolved on the eighth day of hospitalization despite little clinical evidence of improvement. Fluid culture from his bilateral pleural effusion was positive for MRSA and a blood culture on the ninth day of hospitalization was positive for *Aerococcus viridans*. The patient began having negative blood cultures on the tenth day of hospitalization and was extubated on the eleventh.

Anticoagulation was switched to warfarin on the fourteenth day of hospitalization. Erythema tracking along the course of the great saphenous vein was still seen on the sixteenth day of hospitalization (**Figure 2**). However, an ultrasound demonstrated resolution of the femoral vein thrombosis but with complete occlusion of the saphenous-femoral junction. By this time, the patient's respiratory distress had completely resolved, and he was saturating in the high 90's on room air. The patient was treated with antibiotics for 6 weeks and made a full recovery. In the final follow up, the patient was able to return to independent living.

3. Discussion

Case reports of SPE have increased recently in conjunction with a change in etiology [13]. In the 1970's, 76% - 78% of SPE cases were found in intravenous

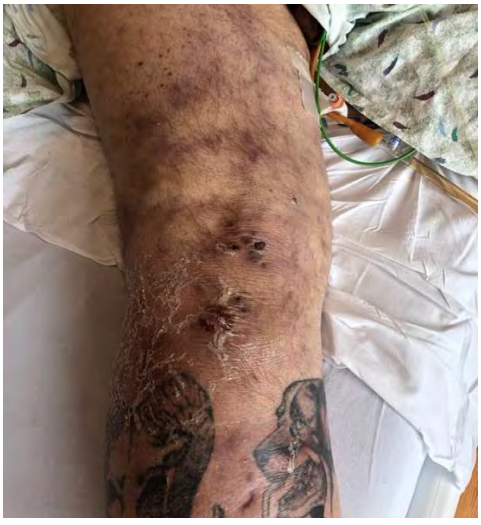


Figure 2. The extremity at day 27 demonstrating thrombus filled great saphenous vein with branches. This venous obstruction of the great saphenous vein developed after thrombosis of femoral vein and during treatment. The healing wounds on the knee are the site of entry of the MRSA into the vascular system.

drug users; this association dropped to 26% in cases reported from 1978-2012 [13] [14] [15]. During this time frame, a majority of SPE cases were caused by *S. aureus* as previously stated. Specific strains of *S. aureus* contain the virulence factor Panton-Valentine Leukocidin (PVL), which is a cytotoxin that destroys leukocytes by its pore forming activity [16]. The presence of the PVL gene is associated with increased virulence, inflammation, and increased rates of ST and is found more commonly in MRSA than methicillin-sensitive *S. aureus* [16] [17]. With the increase in MRSA infections since its emergence in the 1970's, we propose that the increase of case reports could be due to increased rates of MRSA infection resulting in increased SPE rates in the non-intravenous drug using population [18] [19].

The mainstay of treatment for venous thromboembolism due to infectious causes is antibiotics, with or without the use of heparin [20]. There have been a limited number of studies (only one trial consisting of 15 patients) examining the treatment of ST and/or SPE with or without anticoagulation in conjunction with antibiotics with most data being present in the form of case studies. Falagas *et al.* stated that heparin may be used with good outcomes and minimal adverse effects in patients with ST but noted that many patients do well on antibiotics alone. However, our patient already had pulmonary emboli before the time of placement and was therefore restarted on heparin.

Vancomycin has been the mainstay parenteral drug of choice for treatment of MRSA. When started on vancomycin, our patient showed mild improvement by resolution of fever, however he continued to require ventilatory support. This lack of resolution of SPE with vancomycin alone is possibly attributable to its inflammation-dependent, variable tissue penetration and could explain our patient's delayed recovery until after the addition of ceftaroline [21]. An additional regimen that could have been attempted after prolonged MRSA SPE is daptomycin and rifampin. Reports have shown resolution of SPE in patients who fail vancomycin treatment when switched to a combination of daptomycin and rifampin [22].

A thrombectomy with vein excision was considered during the illness. Surgical intervention in patients with septic thrombi who fail to respond to initial medical management can be lifesaving [23]. However, by the time this patient came under our care, his pulmonary emboli had become a nidus of infections; therefore, it was unlikely that removing the septic thrombus in the right leg would have resolved his symptoms. Thus, no surgical intervention was pursued in order to avoid the stress of surgery in a toxic patient.

Previous descriptions of SPE in adults have been associated with either immunologic suppression due to diabetes or intravenous drug abuse. In addition, most cases have been presented with systemic symptoms such as fever, chills, pleuritic chest pain, and dyspnea. The extrapulmonary sources for the pulmonary emboli have been described as coming from pyelonephritis, vertebral osteomyelitis, paraspinal abscesses, pyomyositis, abscess of the thigh, cellulitis, ST, indwelling venous catheters, and endocarditis [9]. Similarly to our patient, patient,

CT scans have often showed cavitary nodules bilaterally, and vegetations were often not present on echocardiogram [9]. Compared to other cases in the literature of SPE, this case is unique in that the source of the septic pulmonary embolus was the superficial femoral vein (**Figure 2**).

In discussing this case, we present it as a patient who has no recent history of intravenous drug abuse. The source of his infection, while still definitively unknown, could have been caused by hitting his leg on the trailer hitch in his garage. He did not report any skin breaks as would be expected to provide an entry for the MRSA. However, there is evidence in the literature that blunt trauma (toe trauma) can result in SPE. Therefore, we propose that our patient's source of infection was likely introduced from his trailer hitch contusion resulting in a soft tissue infection with subsequent development of ST and SPE.

4. Conclusion

SPE is an uncommon disorder with an insidious onset that is difficult to diagnose. We present a case of rapidly progressive SPE from femoral vein thrombophlebitis due to soft tissue injury that required immediate endotracheal intubation and mechanical ventilation. Initial chest CT and X-ray revealed multiple nodular opacities peripherally without cavitation, making the diagnosis difficult in this patient with otherwise normal laboratory values. ST with SPE often presents with protean clinical manifestations and nonspecific radiologic patterns. The diagnosis can be difficult to establish and relies on the presence of a febrile illness, multiple modular lung infiltrates peripherally on CT scan of the chest, and predisposing factors. We describe an unusual case of superficial femoral vein thrombophlebitis causing SPE which required endotracheal intubation and mechanical ventilation due to respiratory failure, which is uncommon in SPE. This case emphasizes the importance of early diagnosis of SPE and appropriate treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Bach, A.G., Restrepo, C.S., Abbas, J., *et al.* (2013) Imaging of Nonthrombotic Pulmonary Embolism: Biological Materials, Nonbiological Materials, and Foreign Bodies. *European Journal of Radiology*, **82**, e120-e141. https://doi.org/10.1016/j.ejrad.2012.09.019

[2] Cook, R.J., Ashton, R.W., Aughenbaugh, G.L. and Ryu, J.H. (2005) Septic Pulmonary Embolism: Presenting Features and Clinical Course of 14 Patients. *Chest*, **128**, 162-166. https://doi.org/10.1378/chest.128.1.162

[3] Alperstein, A., Fertig, R.M., Feldman, M., *et al.* (2017) Septic Thrombophlebitis of the Internal Jugular Vein, a Case of Lemierre's Syndrome. *Intractable & Rare Diseases Research*, **6**, 137-140. https://doi.org/10.5582/irdr.2017.01021

[4] Schubert, A.D., Hotz, M.A., Caversaccio, M.D. and Arnold, A. (2015) Septic Throm-

bosis of the Internal Jugular Vein: Lemierre's Syndrome Revisited. *The Laryngoscope*, **125**, 863-868. https://doi.org/10.1002/lary.24995

[5] Kuhlman, J.E., Fishman, E.K. and Teigen, C. (1990) Pulmonary Septic Emboli: Diagnosis with CT. *Radiology*, **174**, 211-213. https://doi.org/10.1148/radiology.174.1.2294550

[6] Huang, R.M., Naidich, D.P., Lubat, E., Schinella, R., Garay, S.M. and McCauley, D.I. (1989) Septic Pulmonary Emboli: CT-Radiographic Correlation. *American Journal of Roentgenology*, **153**, 41-45. https://doi.org/10.2214/ajr.153.1.41

[7] Iwasaki, Y., Nagata, K., Nakanishi, M., *et al*. (2001) Spiral CT Findings in Septic Pulmonary Emboli. *European Journal of Radiology*, **37**, 190-194. https://doi.org/10.1016/S0720-048X(00)00254-0

[8] Goswami, U., Brenes, J.A., Punjabi, G.V., LeClaire, M.M. and Williams, D.N. (2014) Associations and Outcomes of Septic Pulmonary Embolism. *The Open Respiratory Medicine Journal*, **8**, 28-33. https://doi.org/10.2174/1874306401408010028

[9] Brenes, J.A., Goswami, U. and Williams, D.N. (2012) The Association of Septic Thrombophlebitis with Septic Pulmonary Embolism in Adults. *The Open Respiratory Medicine Journal*, **6**, 14-19. https://doi.org/10.2174/1874306401206010014

[10] Esteves, I., Castro, S.V., Abecasis, F., *et al*. (2010) Septic Pulmonary Embolism Case Report: Optimal Outcome after Insertion of an Inferior Vena Cava Filter in a Patient with *Staphylococcus aureus* Bacteraemia. *International Journal of Pediatrics*, **2010**, Article ID: 651023. https://doi.org/10.1155/2010/651023

[11] Martin, C.A., Wijesurendra, R.S., Borland, C.D. and Karas, J.A. (2007) Femoral Vein Thrombophlebitis and Septic Pulmonary Embolism Due to a Mixed Anaerobic Infection Including *Solobacterium moorei*: A Case Report. *Journal of Medical Case Reports*, **1**, 40. https://doi.org/10.1186/1752-1947-1-40

[12] Harada, K. and Otsuka, F. (2019) Septic Pulmonary Emboli Caused by Infected Central Venous Port. *Postgraduate Medical Journal*, **95**, 282. https://doi.org/10.1136/postgradmedj-2019-136461

[13] Solbeck, S., Meyer, M.A., Johansson, P.I., *et al*. (2014) Monitoring of Dabigatran Anticoagulation and Its Reversal *in Vitro* by Thrombelastography. *International Journal of Cardiology*, **176**, 794-799. https://doi.org/10.1016/j.ijcard.2014.07.084

[14] Jaffe, R.B. and Koschmann, E.B. (1970) Septic Pulmonary Emboli. *Radiology*, **96**, 527-532. https://doi.org/10.1148/96.3.527

[15] MacMillan, J.C., Milstein, S.H. and Samson, P.C. (1978) Clinical Spectrum of Septic Pulmonary Embolism and Infarction. *The Journal of Thoracic and Cardiovascular Surgery*, **75**, 670-679.

[16] Bocchini, C.E., Hulten, K.G., Mason, E.O., Gonzalez, B.E., Hammerman, W.A. and Kaplan, S.L. (2006) Panton-Valentine Leukocidin Genes Are Associated with Enhanced Inflammatory Response and Local Disease in Acute Hematogenous *Staphylococcus aureus* Osteomyelitis in Children. *Pediatrics*, **117**, 433-440. https://doi.org/10.1542/peds.2005-0566

[17] Gonzalez, B.E., Teruya, J., Mahoney, D.H., *et al*. (2006) Venous Thrombosis Associated with Staphylococcal Osteomyelitis in Children. *Pediatrics*, **117**, 1673-1679. https://doi.org/10.1542/peds.2005-2009

[18] Malcolm, B. (2011) The Rise of Methicillin-Resistant *Staphylococcus aureus* in US Correctional Populations. *Journal of Correctional Health Care*, **17**, 254-265. https://doi.org/10.1177/1078345811401363

[19] Rennie, R.P., Jones, R.N., Mutnick, A.H. and Group, S.P.S. (2003) Occurrence and

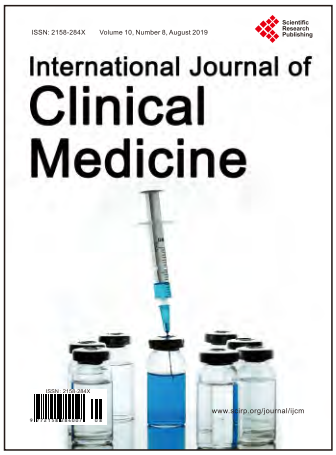
Antimicrobial Susceptibility Patterns of Pathogens Isolated from Skin and Soft Tissue Infections: Report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000). *Diagnostic Microbiology and Infectious Disease*, **45**, 287-293. https://doi.org/10.1016/S0732-8893(02)00543-6

[20] Falagas, M.E., Vardakas, K.Z. and Athanasiou, S. (2007) Intravenous Heparin in Combination with Antibiotics for the Treatment of Deep Vein Septic Thrombophlebitis: A Systematic Review. *European Journal of Pharmacology*, **557**, 93-98. https://doi.org/10.1016/j.ejphar.2006.11.068

[21] Lamer, C., De Beco, V., Soler, P., *et al*. (1993) Analysis of Vancomycin Entry into Pulmonary Lining Fluid by Bronchoalveolar Lavage in Critically Ill Patients. *Antimicrobial Agents and Chemotherapy*, **37**, 281-286. https://doi.org/10.1128/AAC.37.2.281

[22] Gomez, E.O., Jafary, A. and Dever, L.L. (2010) Daptomycin and Rifampin for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Septic Pulmonary Emboli in the Absence of Endocarditis. *Microbial Drug Resistance*, **16**, 241-244. https://doi.org/10.1089/mdr.2010.0001

[23] Kniemeyer, H.W., Grabitz, K., Buhl, R., Wust, H.J. and Sandmann, W. (1995) Surgical Treatment of Septic Deep Venous Thrombosis. *Surgery*, **118**, 49-53. https://doi.org/10.1016/S0039-6060(05)80009-1



Call for Papers

International Journal of Clinical Medicine

ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
http://www.scirp.org/journal/ijcm

International Journal of Clinical Medicine (IJCM) is a peer reviewed journal dedicated to the latest advancement of clinical medicine. The goal of this journal is to keep a record of the state-of-the-art research and to promote study, research and improvement within its various specialties.

Subject Coverage

The journal publishes original papers including but not limited to the following fields:

- Allergy and Clinical Immunology
- Cancer Research and Clinical Oncology
- Clinical Anaesthesiology
- Clinical Anatomy
- Clinical and Applied Thrombosis/Hemostasis
- Clinical and Experimental Allergy
- Clinical and Experimental Dermatology
- Clinical and Experimental Hypertension
- Clinical and Experimental Immunology
- Clinical and Experimental Medicine
- Clinical and Experimental Metastasis
- Clinical and Experimental Nephrology
- Clinical and Experimental Ophthalmology
- Clinical and Experimental Optometry
- Clinical and Experimental Otorhinolaryngology
- Clinical and Experimental Pathology
- Clinical and Experimental Pharmacology and Physiology
- Clinical and Molecular Allergy
- Clinical and Translational Oncology
- Clinical Anesthesia
- Clinical Apheresis
- Clinical Autonomic Research
- Clinical Biochemistry and Nutrition
- Clinical Biomechanics
- Clinical Cardiology
- Clinical Case Studies
- Clinical Child Psychology and Psychiatry
- Clinical Chiropractic
- Clinical Densitometry
- Clinical Effectiveness in Nursing
- Clinical Endocrinology and Metabolism
- Clinical Epidemiology
- Clinical Forensic Medicine
- Clinical Gastroenterology and Hepatology
- Clinical Genetics
- Clinical Haematology
- Clinical Hypertension
- Clinical Imaging
- Clinical Immunology
- Clinical Implant Dentistry and Related Research
- Clinical Interventions in Aging
- Clinical Laboratory Analysis
- Clinical Linguistics & Phonetics
- Clinical Lipidology
- Clinical Microbiology and Antimicrobials
- Clinical Microbiology and Infection
- Clinical Microbiology and Infectious Diseases
- Clinical Molecular Pathology
- Clinical Monitoring and Computing
- Clinical Neurology and Neurosurgery
- Clinical Neurophysiology
- Clinical Neuropsychology
- Clinical Neuroradiology
- Clinical Neuroscience
- Clinical Nursing
- Clinical Nutrition
- Clinical Obstetrics and Gynaecology
- Clinical Oncology and Cancer Research
- Clinical Ophthalmology
- Clinical Oral Implants Research
- Clinical Oral Investigations
- Clinical Orthopaedics and Related Research
- Clinical Otolaryngology
- Clinical Pathology
- Clinical Pediatric Emergency Medicine
- Clinical Periodontology
- Clinical Pharmacology & Toxicology
- Clinical Pharmacy and Therapeutics
- Clinical Physiology and Functional Imaging
- Clinical Practice and Epidemiology in Mental Health
- Clinical Psychology and Psychotherapy
- Clinical Psychology in Medical Settings
- Clinical Radiology
- Clinical Rehabilitation
- Clinical Research and Regulatory Affairs
- Clinical Research in Cardiology
- Clinical Respiratory
- Clinical Rheumatology
- Clinical Simulation in Nursing
- Clinical Sleep Medicine
- Clinical Techniques in Small Animal Practice
- Clinical Therapeutics
- Clinical Toxicology
- Clinical Transplantation
- Clinical Trials
- Clinical Ultrasound
- Clinical Virology
- Complementary Therapies in Clinical Practice
- Consulting and Clinical Psychology
- Contemporary Clinical Trials
- Controlled Clinical Trials
- Diabetes Research and Clinical Practice
- Evaluation in Clinical Practice
- Fundamental & Clinical Pharmacology
- Hereditary Cancer in Clinical Practice
- Human Psychopharmacology: Clinical and Experimental
- Innovations in Clinical Neuroscience
- Laboratory and Clinical Medicine
- Neurophysiologie Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

We are also interested in short papers (letters) that clearly address a specific problem, and short survey or position papers that sketch the results or problems on a specific topic. Authors of selected short papers would be invited to write a regular paper on the same topic for future issues of the ***IJCM***.

Notes for Intending Authors

All manuscripts submitted to IJCM must be previously unpublished and may not be considered for publication elsewhere at any time during IJCM's review period. Paper submission will be handled electronically through the website. All papers are refereed through a peer review process. Additionally, accepted ones will immediately appear online followed by printed in hard copy. For more details about the submissions, please access the website.

Website and E-Mail

http://www.scirp.org/journal/ijcm Email: ijcm@scirp.org

What is SCIRP?

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

What is Open Access?

All original research papers published by SCIRP are made freely and permanently accessible online immediately upon publication. To be able to provide open access journals, SCIRP defrays operation costs from authors and subscription charges only for its printed version. Open access publishing allows an immediate, worldwide, barrier-free, open access to the full text of research papers, which is in the best interests of the scientific community.

- High visibility for maximum global exposure with open access publishing model
- Rigorous peer review of research papers
- Prompt faster publication with less cost
- Guaranteed targeted, multidisciplinary audience

Scientific Research Publishing

Website: http://www.scirp.org

Subscription: sub@scirp.org

Advertisement: service@scirp.org