Current Eye Research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icey20

Acanthamoeba Keratitis: Perspectives for Patients

Stefano Bonini , Antonio Di Zazzo , Giuseppe Varacalli & Marco Coassin

To cite this article: Stefano Bonini , Antonio Di Zazzo , Giuseppe Varacalli & Marco Coassin (2020): Acanthamoeba Keratitis: Perspectives for Patients, Current Eye Research, DOI: 10.1080/02713683.2020.1846753

To link to this article: https://doi.org/10.1080/02713683.2020.1846753

Accepted author version posted online: 05 Nov 2020.

Publisher: Taylor & Francis

Journal: *Current Eye Research*

DOI: 10.1080/02713683.2020.1846753

Acanthamoeba Keratitis: Perspectives for Patients

Stefano Bonini MD[1], Antonio Di Zazzo MD[1], Giuseppe Varacalli MD[1], Marco Coassin MD, PhD[1]

[1]Ophthalmology Complex Operative Unit, University Campus Bio-Medico, Rome, Italy.

Short title: Acanthamoeba Keratitis Clinical Evolution

Authors' contribution:

Designed the analysis: SB. Analyzed the data: all. Contributed materials/analysis tools: SB. Wrote the paper: ADZ and SB.

Keywords: Acanthamoeba keratitis, Prognosis, Treatment, Transplantation

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Corresponding Author:

Prof Stefano Bonini

Ophthalmology Complex Operative Unit

University Campus Bio-Medico

00128 Rome, Italy.

s.bonini@unicampus.it

Abstract

Purpose

To unveil the long-term prognosis of Acanthamoeba keratitis based on clinical presentation and timing of diagnosis to better inform patients since first visit regarding their length of treatment, quality of life, and visual function.

Methods

Retrospective observational study enrolling patients with Acanthamoeba keratitis from 1994 to 2019. Patients with complete eye examination and medical records were analyzed. Severity of the disease, the time from onset of symptoms to the appropriate therapeutic regimen, the time until clinical resolution, visual function, and long-term follow-up were evaluated. Quality of life was assessed at last follow-up visit by means of VFQ-25 questionnaire.

Results:

Thirty-five patients (40 eyes) were assessed. The overall healing time of patients with Acanthamoeba keratitis was 12.5±3.5 months, while patients with a severe corneal ulcer (stage III) had a significant longer healing time (16.2±3.7 months) compared to patients with stage II (7.04±0.7 months) or I (7.7±1.5 months; $p<0.05$). Patients who received a prompt therapy (<30 days form symptoms onset) had a reduced healing time compared to patients with a delayed diagnosis ($p<0.01$). Quality of life was assessed after a mean of 11.7 ±4.7 years and it was mildly reduced (86.6±17). Patients that were diagnosed early (< 30 days from onset) showed a lower reduction in quality of life than in patients that were diagnosed >30 days from onset. After resolution, 59% of patients considered unnecessary any further proposed surgical intervention.

Conclusions:

Delayed diagnosis of Acanthamoeba keratitis and disease severity significantly increase healing time and duration of treatment. The time to diagnosis and disease stage at diagnosis predict the duration of treatment, the final outcome, quality of life, and the requirement of surgery. These data would allow to promptly inform patients about long term disease timeline, future outcomes, improving disease acceptance and quality of life.

Introduction

Corneal damages induced by Acanthamoeba, a free-living ubiquitous protozoan, represent a major challenge for ophthalmologists and their patients' visual function and outcome.[1,2] Corneal ulcers [5,6] caused by Acanthamoeba are responsible for a painful and sight-threatening disease that requires frequent and prolonged, often even surgical, treatment to restore a healthy ocular surface.[1,7–10]

The use of contact lenses is the major risk factor, accounting for 93% of all cases of Acanthamoeba keratitis (AK).[3] The annual incidence of corneal damages has been reported at 0.33 cases per 10.000 contact lens wearers.[3,4] Several variables may influence the outcome of AK: time of diagnosis after first symptoms, different Acanthamoeba strains, individual immune responses, and disease severity.[1,3,8] These variables make it difficult to predict the clinical course of the disease, the frequency and duration of follow-up, and subsequently the patients' quality of life.[11]

In this retrospective study we evaluate how AK patients disease stage, time from onset of keratitis to appropriate treatment, time to clinical resolution, and visual acuity could critically affect healing time, and future risk for surgery since diagnosis. This analysis would allow to promptly inform patients about long term disease timeline, quality of life and future outcomes, improving acceptance of this long course disease.

Patients and Methods

A retrospective case series was conducted on medical records and corneal photographs of patients with AK that had been referred to our tertiary ocular surface center at the University Hospital Campus Bio-Medico of Rome from 1994 to 2012 with 12.2±5.5 (mean±SD; 10 years median) years follow up time. Each patient was evaluated and treated until his cornea was healed and the eye was quite.

Patients with AK were selected based on a culture proven Acanthamoeba infection or histopathological confirmation of trophozoites or cysts, as well as on polymerase chain reaction amoebic specific genome detection.[12–15] Signs and symptoms were recorded and a standard treatment regimen with a combination of 0.1 % propamidine isethionate and 0.02 % polyhexamethylene biguanide was started once the diagnosis was confirmed.[14,16,17] On the basis of their clinical records and corneal images obtained at their first visit a staging of the AK severity was made according to previous reports.[18,19] Briefly, stage I included patients with corneal

epitheliopathy; stage II included patients with corneal epithelial defects and stromal or perineural infiltrates; stage III included patients with 1 or more features of stage 2 plus a corneal ring infiltrate (Fig. 1).[19]

Patients that received a complete eye examination, including corneal photographs in 2019 were analyzed. For those patients with retrievable medical records and previously obtained corneal photographs but unable to come for ocular examination a phone interview was made concerning the development of their disease (relapses, surgical procedures, change in their quality of life and visual acuity if available).

Corneal photographs were taken using a photographic slit lamp (CSO©) at 10x and 16x magnification, according detailed cornea clinic picture acquisition guidelines.

Time from the onset of symptoms to clinical diagnosis was considered time to diagnosis; time from clinical diagnosis to complete corneal healing was considered as resolution of the disease.

Furthermore, all rehabilitation methods were reported, particularly contact lenses or glasses, as well as corneal lamellar or penetrating transplants that were performed.

The measure of the best-available visual acuity (VA) at the last follow-up visit was categorized into 4 grades of visual outcome as previously described[20], grade 1 being a good outcome and denoting final VA 20/30 or better, grade 2 being final VA of 20/40 to 20/60, grade 3 being VA of 20/80 to 20/200, and grade 4 being a poor outcome because of a final VA of worse than 20/200. Patient's quality of life was assessed with the validated questionnaire VFQ-25 in all patients with a final follow-up visit in 2019.[21]

The Ethic Committee of the University Hospital approved the study and the research was conducted in accord with the requirements of the tenets of the Declaration of Helsinki. Study details and potential benefits were thoroughly explained to patients, to whom at last follow up visit in 2019 VFQ-25 questionnaire was administered, and all of them signed an informed consent form before participation in the study.

Patient scores for all outcome variables were calculated by number of involved eyes, with 95% confidence interval for each outcome measure. The differences between stages were assessed using the one-way Anova non-parametric test, while the differences between mean values between the groups were assessed with paired samples t test. A P value of 0.05 was chosen as the limit of statistical significance.

Results

In our retrospective study we evaluated medical records and photographs of 35 patients (40 eyes) referred to our tertiary ocular surface center at the University Hospital Campus Bio-Medico of Rome from 1994 to 2012. The demographic characteristics of 27 included patients are reported in Table 1. 18% of all patients had AK in both eyes. The mean age at onset of AK was 30±13 years (male 32±15 yrs; female 28±13 yrs). Most eyes (47%) were classified as stage III. 87% of all patients had a central corneal infection, while the paracentral cornea was involved in only 17.3 % of all eyes.

We found in 27 patients (31 eyes) an overall mild reduction of quality of life (Score: 80.6±17/100). Patients that were diagnosed early (<30 days form symptoms onset) represented with a better quality of life than patients diagnosed >30 days after first symptoms (Fig. 2).

The mean healing time, i.e. from beginning of treatment to clinical resolution, was 12.5±3.5 months, with a 7 months median. Patients presenting with a severe corneal ulcer (stage III) had a significant longer healing time (16.2±3.7 months) compared to patients with stage II (7.04±0.7 months) or stage I (7.7±1.5 months; $p<0.05$; Fig. 3A). Patients who received a prompt Acanthamoeba therapy (<30 days form symptoms onset) represented with a significant lower healing time compared to patients with a delayed diagnosis (>30 days form symptoms onset; Fig. 3B; $p<0.01$).

Seventy percent of the patients with severe residual outcome (grade IV AK) [20] showed severe visual impairment even after clinical resolution (Fig. 4A). To restore visual function, 41% of all patients required corneal surgery. Fifty-nine percent of the patients despite visual impairment considered unnecessary further surgical procedures. Visual acuity slighty decreased in these unoperated patients (LogMar 0.13±0.1; Table 1). 53% of patients with advanced stage III required corneal transplantation to achieve a good visual outcome (Fig. 4B). Only 1 patient with early disease stage required surgery.

Discussion

We found that the ophthalmologist can predict AK treatment duration, healing process and clinical outcomes at patient's first visit. Particularly, time of diagnosis (< or > 30 days from symptoms onset) and disease severity help predict treatment duration, possible outcome, and need for surgery. These data critically impact patient compliance to advised treatment, professional and personal future choices, as well as quality of life – especially in this young age group. Interestingly, majority of patients considered unnecessary further surgical procedure that we proposed after infection resolution. Quality of life was only mildly reduced when assessed after more than a decade from clinical resolution.

The high rate of patients with late stage AK suggests a current trend of misdiagnosis, which ultimately affects patient care and prognosis. A prompt diagnosis and start of therapeutic treatment significantly improves corneal healing and reduces the risk of surgical procedures. Here, we report that corneal ulcers induced by Acanthamoeba require a mean time of 12.5 months to heal and to restore the ocular surface. Patients presenting with severe corneal ulcers require an even longer treatment. In addition, we show that patients with severe AK had longer follow-ups compared to patients with stage I or II. Our data confirm previous reports by Carnt et al.[22] indicating that patients with AK require 10 months of treatment with 38 months of follow-up and a mean number of 31 visits to restore their ocular surface. In spite of this, they may end up with poor vision requiring corneal transplantation.[23] In our study 41% of all patients, although treated, required a corneal surgical procedure, probably due to a higher paracentral incidence of AK in stage II and I. In fact, among enrolled eyes 46.8% were severe cases with corneal rings and intense inflammation. Patients with mild (stage 1) or moderate (stage II) disease had a better prognosis and final outcome. Thus, an early diagnosis improves the visual outcome and reduces the need for additional surgeries.[24,25]

Surgical procedures have been frequently reported as a consequence of permanent corneal damage due to AK.[26,27] In our study all patients, who required transplant surgery, had a poor or very poor outcome according Dart staging,[20] mainly related to the advanced stage before the surgery, as well as, to the central corneal localization of the disease at diagnosis. Only one patient with early stage AK and Dart grade 1 received surgery because of the bilateral central corneal infection.

In our patients, quality of life was possibly reduced because of their long and painful treatment as well as the frequent follow-up visits until clinical resolution, which often takes months. Moreover, bilateral corneal

damage as well as a permanent functional damage in severe cases further reduces the quality of life. In addition, the mindfulness of disease timing and timeline as well as the need for intense treatment or complex surgery limit patient personal future life and working choices. Thus, the major impact on quality of life is not only related to the sequelae of AK, but to the long healing time, which is characterized by severe daily pain with relapsing acute episodes as well as a frequent treatment and follow-up protocol.

Our study limitations are the low number of patients as compared to previous report as well as the retrospective method of analysis. In one elderly patient, age could have influenced his answers to quality of life questionnaire.

In summary, a prompt diagnosis reduces the need for prolonged medical treatment and for surgical procedures. Mildly reduced quality of life in the long term might endorse patitents' choice to not consenting to corneal transplant as we recommend after infection resolution. The time to diagnosis from first symptoms and disease severity (disease stage) predicted healing process, duration of treatment, visual outcome and risk of surgery. These data would allow to promptly inform patients about their long-term disease timeline and future outcomes, improving disease acceptance . This information can support patients in making personal and work-related life choices, and help to increase the compliance to a long, intense, and painful treatment.

Disclosure:

Authors declare no conflict of interest.

Acknowledgments:

The authors would like to thank Dr. Susanne Eiglmeier for writing assistance and proofreading the manuscript.

References:

1. Stapleton F, Ozkan J, Jalbert I, Holden BA, Petsoglu C, McClellan K. Contact Lens-Related Acanthamoeba Keratitis. Optom Vis Sci. 2009;86(10):1196-1201.

2. Szentmáry N, Daas L, Shi L, et al. Acanthamoeba keratitis – Clinical signs, differential diagnosis and treatment. J Curr Ophthalmol. 2019;31(1):16-23.

3. Radford CF, Lehmann OJ, Dart JK. Acanthamoeba keratitis: multicentre survey in England 1992-6. National Acanthamoeba Keratitis Study Group. Br J Ophthalmol. 1998;82(12):1387-1392.

4. Seal DV. Acanthamoeba keratitis update - Incidence, molecular epidemiology and new drugs for treatment. Eye. 2003;17(8):893-905.

5. Cheng KH, Leung SL, Hoekman HW, Beekhuis WH, Mulder PG, Geerards AJ, Kijlstra A. Incidence of contact-lens-associated microbial keratitis and its related morbidity. Lancet. 1999;354(9174):181-185.

6. Radford CF, Minassian DC, Dart JK. Acanthamoeba keratitis in England and Wales: Incidence, outcome, and risk factors. Br J Ophthalmol. 2002;86(5):536-542.

7. Sivak JM, Fini ME. MMPs in the eye: emerging roles for matrix metalloproteinases in ocular physiology. Prog Retin Eye Res. 2002;21(1):1-14.

8. Carnt N, Stapleton F. Strategies for the prevention of contact lens-related Acanthamoeba keratitis: A review. Ophthalmic Physiol Opt. 2016;36(2):77-92.

9. Carnt N, Robaei D, Minassian DC, Dart JKG. Acanthamoeba keratitis in 194 patients: Risk factors for bad outcomes and severe inflammatory complications. Br J Ophthalmol. 2018;102(10):1431-1435.

10. Qian Y, Meisler DM, Langston RHS, Jeng BH. Clinical Experience With Acanthamoeba Keratitis at the Cole Eye Institute, 1999-2008. Cornea. 2010;29(9):1016-1021.

11. Claerhout I, Goegebuer A, Van Den Broecke C, Kestelyn P. Delay in diagnosis and outcome of Acanthamoeba keratitis. Graefe's Arch Clin Exp Ophthalmol. 2004;242(8):648-653.

12. Bacon AS, Dart JKG, Ficker LA, Matheson MM, Wright P. Acanthamoeba Keratitis: The Value of Early Diagnosis. Ophthalmology. 1993;100(8):1238-1243.

13. Tu EY, Joslin CE, Sugar J, Shoff ME, Booton GC. Prognostic Factors Affecting Visual Outcome in Acanthamoeba Keratitis. Ophthalmology. 2008;115(11):1998-2003.

14. Elder MJ, Kilvington S, Dart JKG. A clinicopathologic study of in vitro sensitivity testing and Acanthamoeba keratitis. Investig Ophthalmol Vis Sci. 1994;35(3):1059-1064.

15. Boggild AK, Martin DS, Lee TYL, Yu B, Low DE. Laboratory diagnosis of amoebic keratitis: Comparison of four diagnostic methods for different types of clinical specimens. J Clin Microbiol. 2009;47(5):1314-1318.

16. Dart JKG, Saw VPJ, Kilvington S. Acanthamoeba Keratitis: Diagnosis and Treatment Update 2009. Am J Ophthalmol. 2009;148(4):487-499.e2.

17. Yamazoe K, Yamamoto Y, Shimazaki-Den S, Shimazaki J. Visual outcome in Japanese patients with Acanthamoeba keratitis. Eye. 2012;26(4):517-522.

18. Parmar DN, Awwad ST, Petroll WM, Bowman RW, McCulley JP, Cavanagh HD. Tandem Scanning Confocal Corneal Microscopy in the Diagnosis of Suspected Acanthamoeba Keratitis. Ophthalmology. 2006;113(4):538-547.

19. Robaei D, Carnt N, Minassian DC, Dart JKG. The impact of topical corticosteroid use before diagnosis on the outcome of Acanthamoeba keratitis. Ophthalmology. 2014;121(7):1383-1388.

20. Robaei D, Carnt N, Minassian DC, Dart JKG. Therapeutic and optical keratoplasty in the management of Acanthamoeba keratitis: Risk factors, outcomes, and summary of the literature. Ophthalmology. 2015;122(1):17-24.

21. Balcer LJ, Baier ML, Kunkle AM, Rudik RA, Weinstock-Guttan B, Simonian N, Galetta SL, Cutter GR, Maguire MG. Self-reported visual dysfunction in multiple sclerosis: Results from the 25-Item National Eye Institute Visual Function Questionnaire (VFQ-25). Mult Scler. 2000;6(6):382-385.

22. Carnt N, Hoffman JJ, Verma S, Hau S, Radfor CF, Minassian DC, Dart JKG. Acanthamoeba keratitis: Confirmation of the UK outbreak and a prospective case-control study identifying contributing risk factors. Br J Ophthalmol. 2018;102(12):1621-1628.

23. Kitzmann AS, Goins KM, Sutphin JE, Wagoner MD. Keratoplasty for Treatment of Acanthamoeba Keratitis. Ophthalmology. 2009;116(5):864-869.

24. Kaiserman I, Bahar I, McAllum P, Srinivasan S, Elbaz U, Slomovic AR, Rootman DS. Prognostic factors in Acanthamoeba keratitis. Can J Ophthalmol. 2012;47(3):312-317.

25. Bouheraoua N, Gaujoux T, Goldschmidt P, Chaumeil C, Laroche L, Borderie VM. Prognostic factors associated with the need for surgical treatments in Acanthamoeba Keratitis. Cornea. 2013;32(2):130-136.

26. Awwad ST, Parmar DN, Heilman M, Bowman RW, McCulley JP, Cavanagh HD. Results of penetrating keratoplasty for visual rehabilitation after Acanthamoeba keratitis. Am J Ophthalmol. 2005;140(6).

27. Shimmura-Tomita M, Takano H, Kinoshita N, Toyoda F, Tanaka Y, Takagi R, Kobayashi M, Kakehaschi A. Risk factors and clinical signs of severe acanthamoeba keratitis. Clin Ophthalmol. 2018;12:2567-2573.

Figure Legends:

Fig. 1. Representative slit lamp pictures showing the clinical development of a female patient wearing contact lenses with Acanthamoeba keratitis. Images showing (A) a central corneal ulcer with mild opacity in the corneal stroma (Stage I), (B) an initial corneal ring (Stage II), (C) a complete corneal ring with a corneal epithelial ulcer and corneal stroma opacity (Stage III) Images were taken with a CSO SL, 10x magnification.

Fig. 2. The time of diagnosis and disease severity of acanthamoeba keratitis determine the healing time. (A) Corneal healing time (months) from diagnosis to resolution of the disease is shown according to (A) disease stage and (B) time of diagnosis (< vs. > 30 days from symptoms onset). ANOVA, *$p<0.05$; ** $p<0.01$; *** $p<0.001$.

Fig. 3. The disease severity determines the final visual outcome and the need of surgery. (A) Functional visual outcome of patients according to their disease stage is shown. (B) Rate of patients that received surgery (transplantation) according to their disease stage. ANOVA *$p<0.05$; ** $p<0.01$; *** $p<0.001$.

Fig. 4. Quality of life in patients with Acanthamoeba keratitis depends on time of diagnosis. Results from a VFQ-25 quality of life questionnaire are shown based on time of diagnosis (< vs. > 30 days from symptoms onset). Student t test*$p<0.05$; ** $p<0.01$; *** $p<0.001$.

Table 1. Patients' Characteristics

PT NUMBER	GENDER	AGE AT ONSET	INVOLVED EYE	CLINICAL STAGE (I-II-III)	HEALING TIME (MO)	TIME TO DIAGNOSIS (MO)	VISUAL ACUITY (LOGMAR)
1	M	54	OD	III	-	-	-
2	M	21	OS	III	18	3	0
3	M	67	OS	III	-	-	-
4	M	29	OS	I	-	-	-
5	F	29	OD	I	7	1	0
6	M	29	OD	II	-	-	-
7	M	16	OD	I	-	-	-
8	F	12	OD	II	8	2	0.1
9	M	20	OS	II	11	8	0.2
10	M	41	OD	II	5	1	0
11	M	47	OD	III	5	1	0.1
12	F	26	OD	III	36	12	0
			OS	III	36	12	0
13	F	26	OD	II	6	1	0.1
14	M	25	OD	II	7	1	0
15	F	41	OD	III	-	-	-
16	M	28	OS	II	2	1	0.3
17	F	24	OD	II	10	4	0.1
18	F	14	OS	II	7	1	0.1
19	M	46	OD	III	5	1	0.1
			OS	I	5	1	0.3
20	F	45	OD	III	4	1	0.3
21	F	42	OD	III	12	3	1
			OS	I	12	3	0
22	M	29	OS	III	-	-	-
23	F	44	OD	II	5	1	0.1
24	M	20	OD	III	12	3	0.1
			OS	I	7	2	0.1
25	F	21	OD	III	22	3	0
26	F	14	OD	III	12	1	0.3
27	M	18	OD	II	-	-	-

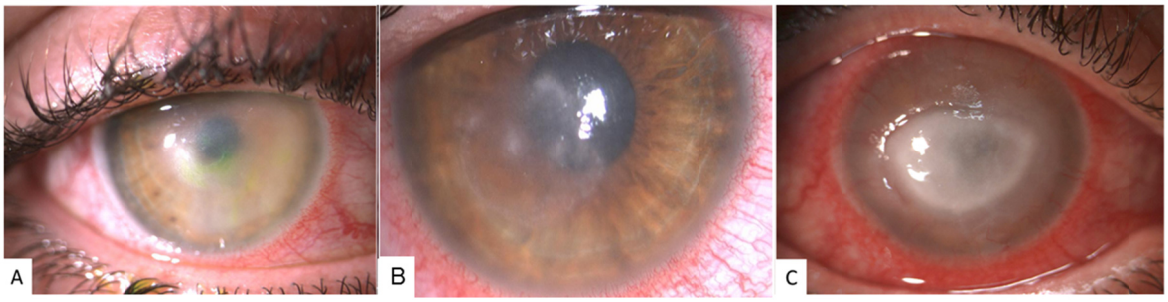

Figure 1

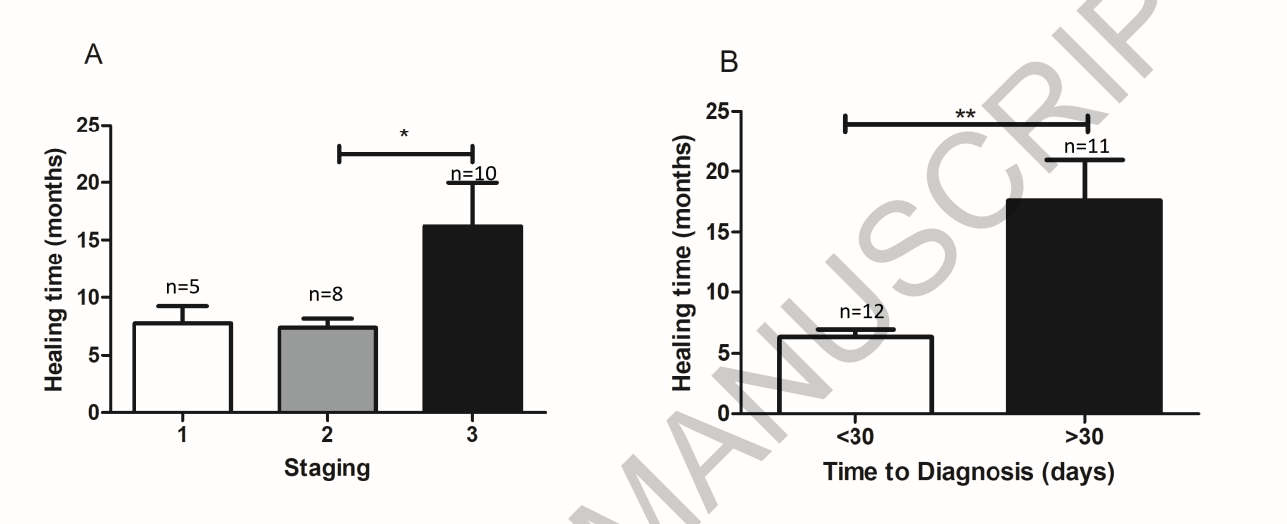

Figure 2

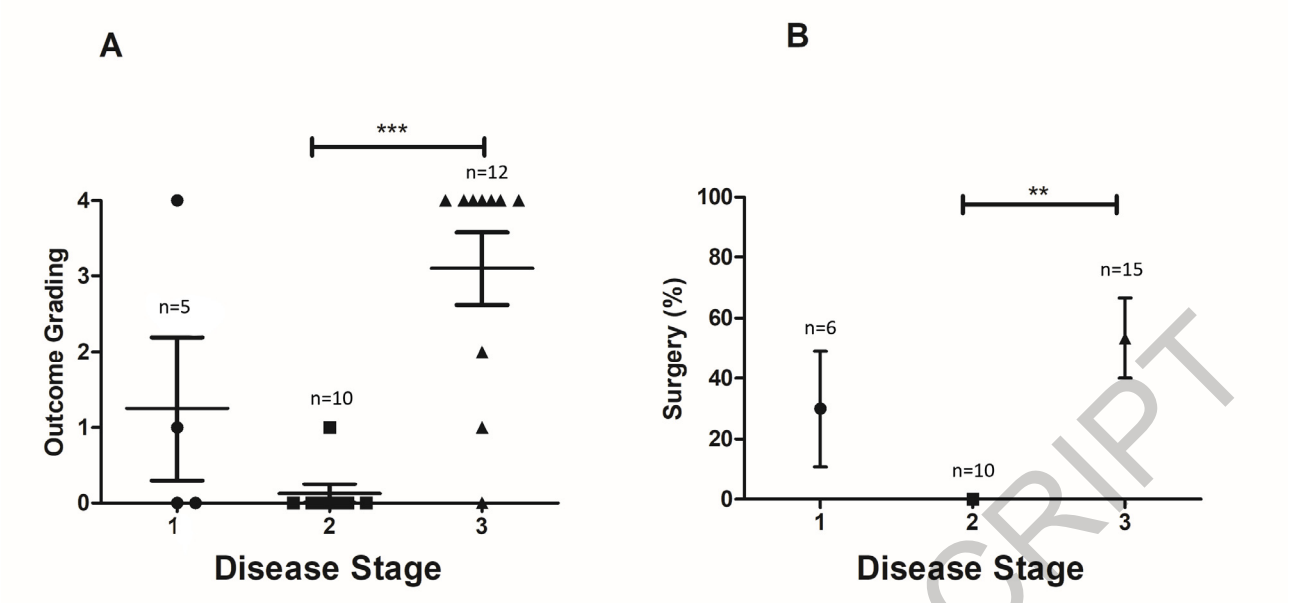

Figure 3

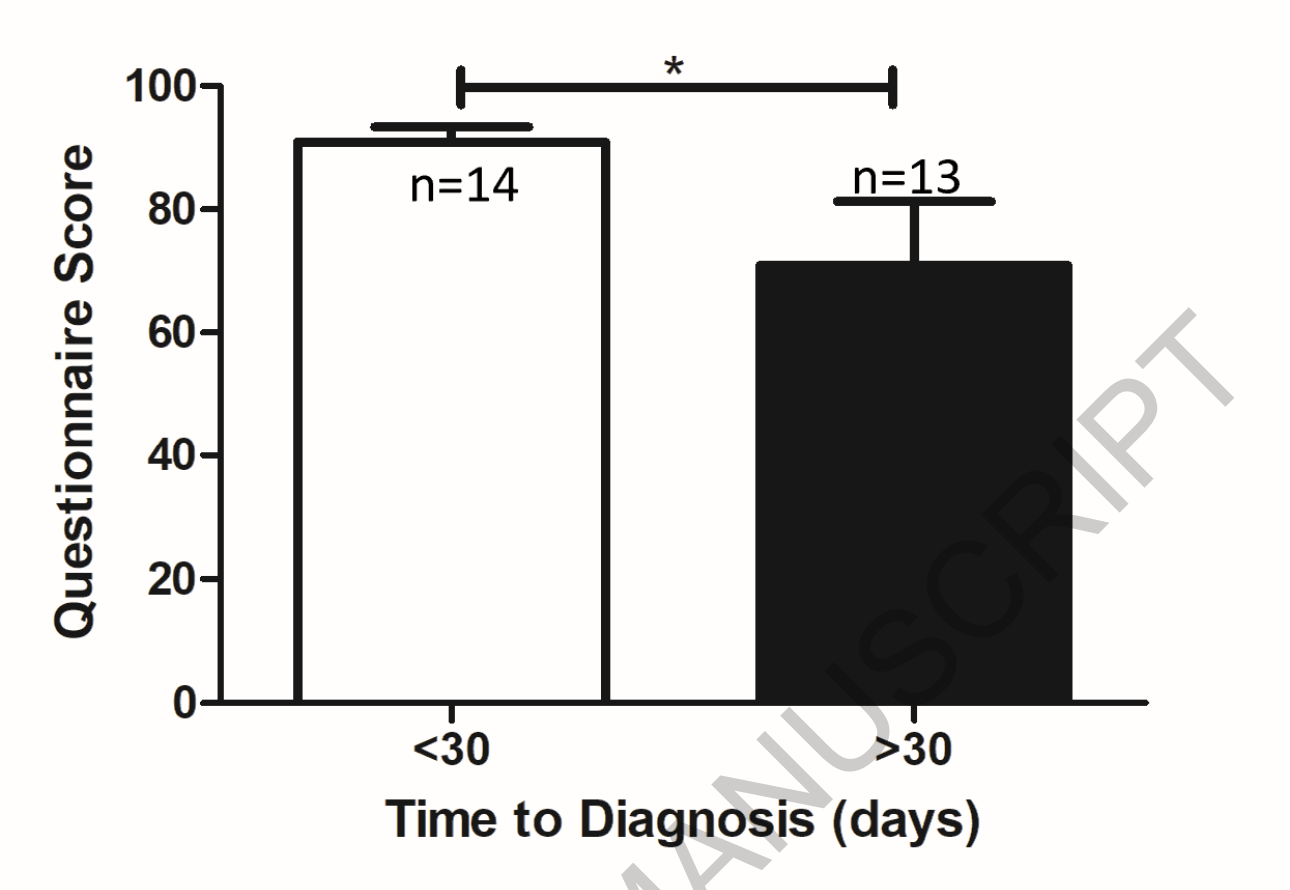

Figure 4