

Cryptococcosis in Patients with Cirrhosis: A Review of Cryptococcal Cases Among Hospitalized Patients from 1992-2013 at an Academic Transplant Center in Massachusetts

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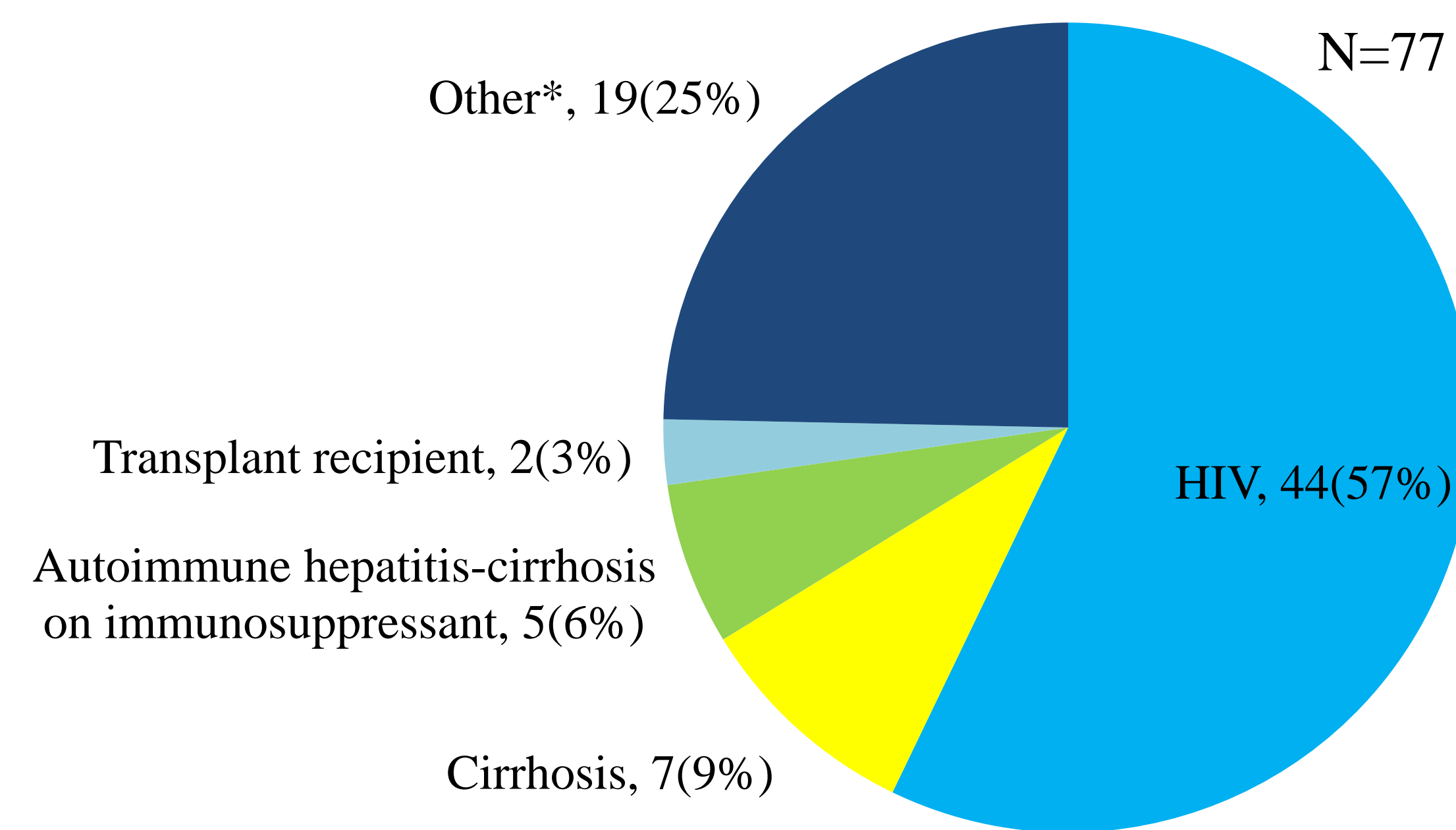
INTRODUCTION

Cirrhosis is a recognized risk factor for cryptococcal infection and published case series indicate high mortality in this setting. Limited data are available comparing the clinical features and outcomes of cryptococcosis in patients with cirrhosis vs. patients with other underlying risk factors. The purpose of this study is to describe and compare the clinical presentation and outcomes of cryptococcal infection among cirrhotic vs. non-cirrhotic patients.

METHODS

Patients with cryptococcosis hospitalized at UMass Memorial Medical Center in Worcester, MA from January 1992 to April 2013 were identified using ICD-9 codes (117.5 cryptococcosis and 321.0 cryptococcal meningitis) and microbiology and pathology databases. Annual changes in frequency of cryptococcal infection, patient demographics, underlying risk factors, etiology of liver disease if present, symptoms, microbiology, treatment, side effects and outcome information were collected and compared among patients with and without cirrhosis.

RESULTS



CRYPTOCOCCOSIS IN CIRRHOSIS

Case	Age Sex	Cirrhosis cause (Medication) MELD ^a Score	Organ involved	Clinical presentation	Diagnosis	Treatment	OLT	Outcome
1	47 F ^b	Autoimmune hepatitis (unknown) MELD 22	Lung	Incidental lung nodule	pathology	Lung resection AmpBd ^d 3 days → fluconazole 6 month	Yes	OLT in 8 months, mild rejection in 5 years
2	46 F	Autoimmune hepatitis, UC ^c (AZA ^e 50mg/day) MELD 16	CNS ^f	Headache, Blurry vision, Pancytopenia, GIB ^g	Serum antigen CSF antigen CSF culture	AmpBd +5FC ^h → LF AmpB ⁱ + 5FC → fluconazole	No	Listed for OLT Died in 2 months
3	66 F	Autoimmune hepatitis, SLE ^j (Pred ^m) MELD 33	CNS	Fever, confusion, headache, seizure, hypotension, GIB, AKI ⁿ	Serum antigen CSF antigen Blood culture CSF culture	LF AmpB + 5FC	No	Listed for OLT Died in 1 month
4	65 F	Autoimmune (Pred 20mg/day) MELD 38	Antigenemia	Hypotension, AKI, Rt lung apical granuloma	Serum antigen (1:4)	Fluconazole 3 weeks	Yes	Negative titer in 1 week, OLT in 3 weeks, doing well
5	55 M ^c	Autoimmune, 1 ^o Biliary Cirrhosis (Pred 30mg/day + AZA) MELD 20	CNS	Fever, headache, hypotension, pancytopenia	Serum antigen CSF antigen Blood culture CSF culture	Ampho B + 5FC → LF AmpB + 5FC → fluconazole	No	Died of gram negative sepsis in 2 month
6	59 F	Alcohol MELD 8	CNS	Seizure, confusion	Serum antigen CSF antigen CSF culture	AmpBd + 5FC → LF AmpB + 5FC then fluconazole	No	Improved Loss follow up
7	51 M	Alcohol, HCV ^o , HCC ^p MELD 16	Lung	Leukocytosis, Lung nodule	Pathology, Tissue culture	Fluconazole indefinitely	Yes	OLT in 4 months, died 2 months after from gram negative sepsis
8	55 M	HBV ^q , HCV MELD 16	CNS	Fever, confusion, hypotension, pancytopenia	CSF antigen CSF culture	AmpBd + 5FC → LF AmpB+5FC → fluconazole	No	Listed for OLT Died in 2 months
9	44 F	HCV, Splenectomy MELD 22	CNS	Fever, headache, confusion, GIB	Serum antigen CSF antigen CSF culture	LF AmpB + 5FC → fluconazole	No	Listed for OLT Died in 2 months
10	57 F	HBV, HDV ^r MELD 28	CNS	Fever, headache, hypotension, confusion, GIB	Serum antigen CSF antigen CSF culture	LF AmpB + 5FC → fluconazole	No	Listed for OLT Died in 2 months
11	62 F	NASH ^s MELD 38	Antigenemia	Hypotension, leukocytosis, GIB	Serum antigen (1:32 → 1:128)	Fluconazole	Yes	OLT in 6 weeks, PTL ^t
12	56 F	HCV, Alcohol MELD 26	Fungemia	Confusion, pancytopenia, GIB	Serum antigen (1:4096) Blood culture	LF AmpB → fluconazole	No	Died in 2 months No lumbar puncture done

Table 1 Review of cryptococcosis cases among cirrhosis patients and liver transplant candidates

OLT: orthotopic liver transplant, ^a Model for End-Stage Liver Disease (MELD) score, ^bfemale, ^cmale, ^d amphotericin B deoxycholate, ^e ulcerative colitis, ^f Azathioprine, ^g central nervous system, ^h gastrointestinal bleeding, ⁱ cerebrospinal fluid, ^j flucytosine, ^k lipid based amphotericin B, ^l systemic lupus erythematosus, ^m prednisone, ⁿ acute kidney injury, ^o hepatitis C virus infection, ^p hepatocellular carcinoma, ^q hepatitis B virus infection, ^r hepatitis D virus infection, ^s non-alcoholic steatohepatitis, ^t post-transplant lymphoproliferative disorder

CIRRHOSIS VS NON-CIRRHOSIS

Category	Total N = 77(%)	Non-cirrhosis N = 65(%)	Cirrhosis N = 12(%)	p-value*
Demographics				
Median age, years (range)	44(22-84)	42(22-84)	56(44-66)	0.003
Organ affected				
CNS** involvement	59(77)	52(68)	7(58)	0.13
Pulmonary cryptococcosis	12(15)	10(15)	2(17)	1.00
Cryptococemia	3(4)	2(3)	1(8)	0.40
Antigenemia	3(4)	1(2)	2(17)	0.06
Presentation				
Asymptomatic	6(8)	4(6)	2(17)	0.55
Fever	39(51)	34(52)	5(42)	0.54
Altered mental status	29(38)	22(34)	7(58)	0.19
Hypotension	10(13)	4(6)	6(50)	0.0006
Leukocytosis/leukopenia	49(64)	40(62)	9(75)	0.51
Renal insufficiency	15(19)	7(11)	8(67)	0.0001
Gastrointestinal bleeding	8(10)	1(2)	7(58)	0.0001
Severity				
Severe	61(79)	53(82)	8(67)	0.25
Induction treatment				
AmpBd*** based regimen	46(59)	42(65)	4(33)	0.06
LF AmpB**** based regimen	21(27)	16(25)	5(42)	0.29
Fluconazole	10(13)	7(11)	3(25)	0.18
Treatment side effects				
None	40(52)	37(57)	3(25)	0.06
Renal insufficiency	23(30)	15(23)	8(67)	0.004
Hematologic side effect	7(9)	6(9)	1(8)	1.0
Change medication from side effect	14(18)	8(12)	6(50)	0.006
Mortality				
2 month mortality	16(21)	9(14)	7(58)	0.002
1 year mortality	20(26)	12(18)	8(67)	0.001

Table 2 Comparison between cirrhosis and non-cirrhosis patients with cryptococcosis

* Statistical analysis done by using Stata/IC (Stata Corp College Station, TX) : Fisher exact test for categorical variables and Mann-Whitney test for continuous variables, p-value of ≤ 0.05 was considered to be statistically significant
** central nervous system
*** amphotericin B deoxycholate
**** lipid based amphotericin B

EPIDEMIOLOGICAL CONTRIBUTION

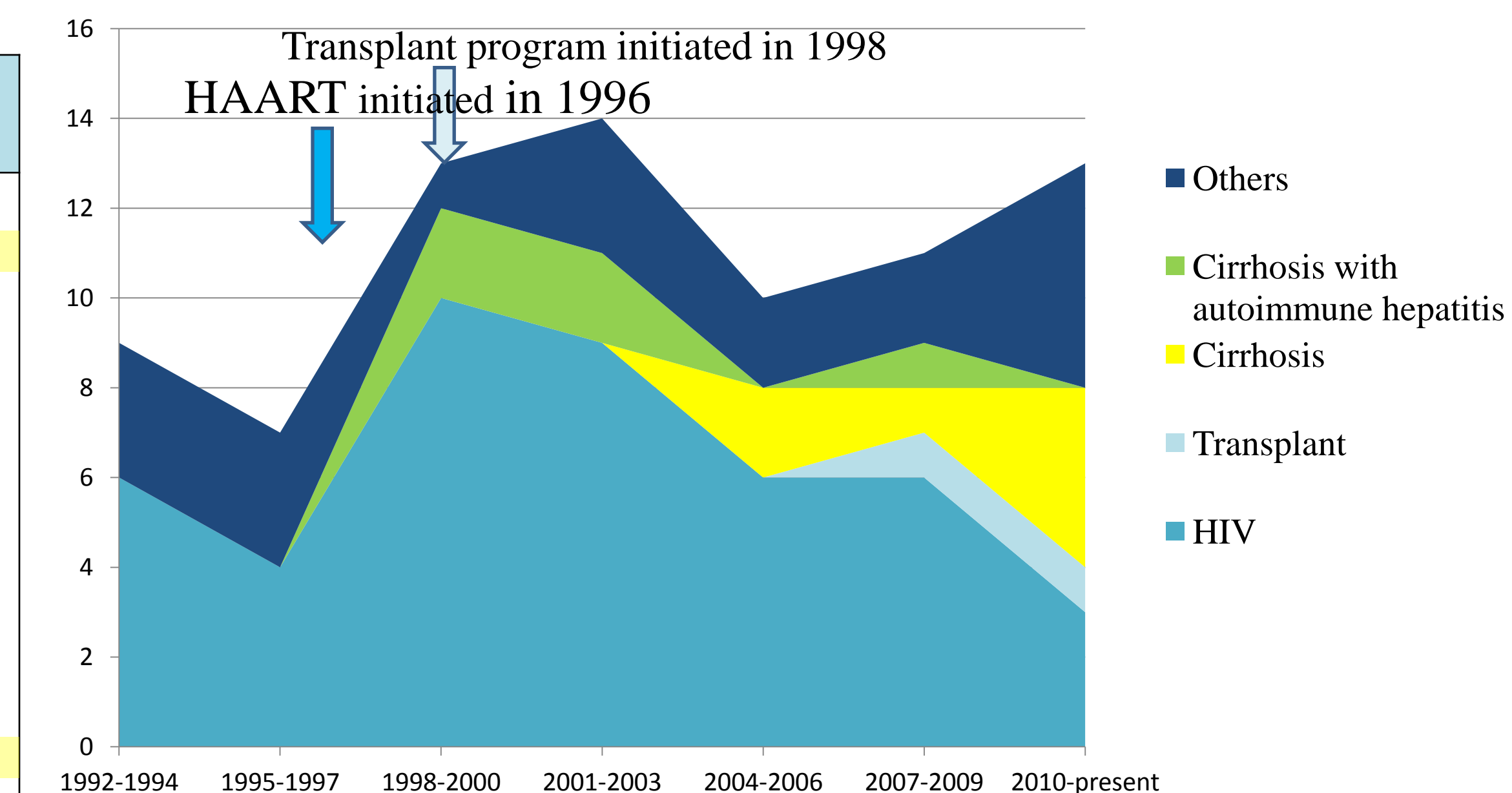


Figure 2 Epidemiologic distribution of cryptococcosis among different underlying disease groups over 22 years

CONCLUSION

In our single center experience, cirrhotic patients with cryptococcal infection have certain distinct clinical manifestations and complications associated with treatment compared with non-cirrhotics. We acknowledge that these distinct features are seen in ESKD alone and the relative contribution of ESKD and cryptococcosis could not be determined. We observed high mortality in cirrhotic patients with cryptococcosis, however in some patients, especially those with non-severe disease, this diagnosis does not seem to preclude eventual successful liver transplant.

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