厚生労働科学研究費補助金（肝炎等克服政策研究事業）
令和２年度　分担研究報告書
肝炎ウイルス感染状況の把握及び肝炎ウイルス排除への方策に資する疫学研究

# C 型肝炎ウイルス排除後に初発した肝細胞癌の特徴と予後

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**研究要旨**

大垣市民病院および協力研究施設 14 施設において、C 型肝炎ウイルス（HCV）に対する経口抗ウイルス療法（DAA）施行前には肝細胞癌（HCC）の既往がなく、抗ウイルス療法により HCV 排除（SVR）がなされた後に肝細胞癌が初発で発生した症例を集積し、従来の HCV 持続感染中に発生した肝細胞癌とその特徴・予後を比較した。当院を加えた 15 施設からの SVR 後初発 HCC は 181 例であった。これを 2011～2015 年に大垣市民病院・愛媛県立中央病院で HCV 持続感染中に発生した HCC 中、残存肝機能が Child-Pugh class A であった 215 例と比較すると、HCC のサーベイランス下で発見された HCC は SVR 例で 178/181 例（98.3％）、HCV 持続感染例で 127/215 例（59.1％）と前者で有意に高かった（p<0.0001）。サーベイランス下で発見された HCC に限定して比較したが、診断時の HCC は SVR 例で有意に腫瘍径が小さく、単発例の割合が高く、AFP 低値とより早期な症例が多かった。また診断時の肝機能は SVR 例で有意に良好であった。初発 HCC 診断後の生存率を見ると、SVR 例で有意に高く（p<0.0001）、propensity score matching で両群の腫瘍進行度・肝機能を揃えても同様であった（p=0.0174）。多変量解析では、SVR は HCC 治療後の高い生存率に有意に関連した（p<0.0001）。一方、根治治療例における治療後再発率は両群間で差を認めなかった（p=0.7484）。初発診断時と再発時の肝機能を ALBI score で比較すると、SVR 例では再発時の ALBI score は初発時より低く肝機能が改善しているのに対し、HCV 持続感染例では再発時に肝機能は悪化していた。この結果再発に対して根治治療が施行できた割合は SVR 症例で有意に高く（p=0.0008）、その後の生存率は有意に良好であった（p=0.0087）。

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## A. 研究目的

C 型慢性肝炎症例においては、直接作動型抗ウイルス薬（DAAs）の臨床使用により、ほぼ全例で C 型肝炎ウイルス（HCV）の排除（SVR）が可能となった。一方で、SVR 後に発生する肝細胞癌（HCC）症例の増加が昨今問題となっている。これら肝細胞癌の既往がなく、SVR 後に初発する肝細胞癌が多く報告されている一方で、その特徴・予後はまだ十分明らかにされていない。このため、SVR 後に HCC が発生してしまった症例でも SVR を達成したことに生命よごに対するベネフィットがあったのかも検証は不十分である。

今回の検討では SVR 後初発肝細胞癌を HCV 持続感染中に発生した HCC と比較することにより、新しい成因としての「SVR 後 HCC」の特徴・予後を明らかにすることを目的とした。

## B. 研究方法

当院および共同研究施設 14 施設（愛媛県立中央病院・北里大学病院・横浜市立大学市民医療センター・おおたかの森病院・香川県立中央病院・新松戸中央総合病院・日本医科大学病院・名古屋市立大学病院・済生会新潟病院・キッコーマン総合病院・聖マリアンナ医科大学病院・旭中央病院・手稲渓仁会病院・日本医科大学千葉北総病院）において DAAs 治療により HCV 排除（SVR）を達成した HCC 既往のない 5270 例中、SVR 後に初発 HCC の発生を認めた 181 例について検討した。対象として大垣市民病院・愛媛県立中央病院で 2011～2015 年に診断された HCV 持続感染中に発生した HCC で肝機能が Child-Pugh class A で

あった 215 例と比較した。検討内容として、初発診断時の HCC の進行度･残存肝機能､診断後の生存率、根治治療例の再発率、再発治療後の生存率等を解析した。

## C. 研究結果

①SVR 後 HCC と HCV 持続感染 HCC の比較

まず、初発 HCC 診断時の状況を比較すると、サーベイランス下で発見された HCC は SVR 例で 181 例中 178 例（98.3%）、HCV 持続感染例で 215 例中 127 例（59.1%）と前者で有意に高かった（p<0.0001）。一般にサーベイランスされていない状態で発見・診断された HCC は進行していることが多く予後不良なため、以下はサーベイランス下で発見・診断された HCC（SVR 例 178 例・HCV 持続感染例 127 例）を比較した。診断時の特徴を比較すると（表 1）、SVR 例において、HCC の最大腫瘍径は有意に小さく（p=0.0002）、単発症例の割合が有意に高かった（p=0.0008）。また HCC の腫瘍マーカーである AFP・AFP-L3 は有意に低かった（いずれも p<0.0001）。残存肝機能を比較すると、いずれの群も全例 Child-Pugh class A の症例であったが、より細かく残存肝機能を反映する ALBI score を比較すると SVR 例で有意に低く（ALBI score は低値なほど肝機能が良好)、肝機能は良好であった。一方、根治治療（肝切除または経皮的局所療法）を施行された症例の割合は同等であった（p=0.6512)。

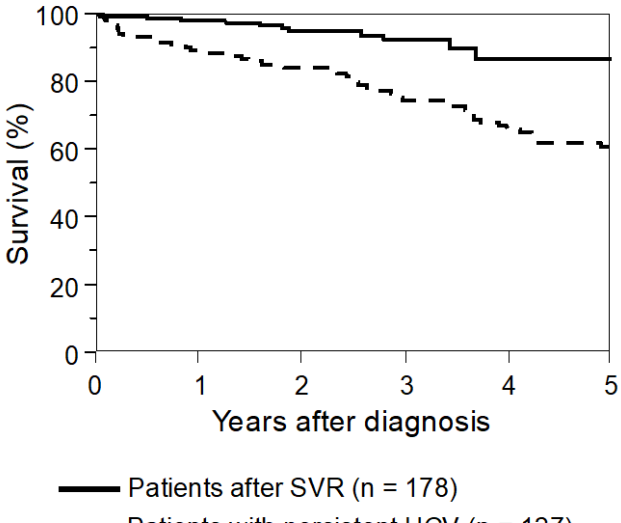
表 1 ：SVR後初発HCCとHCV持続感染中HCCの比較

| | HCC after SVR (n = 178) | Control (n = 127) | p value |
|---|---|---|---|
| Age (years, median) | 72 (66, 78) | 74 (69, 79) | 0.0555 |
| Gender (male/female) | 120 (67.4) / 58 (32.6) | 81 (63.8) / 46 (36.2) | 0.5412 |
| HBsAg (negative/positive) | 173 (97.2) / 5 (2.8) | 123 (96.9) / 4 (3.2) | 1.0000 |
| Habitual alcohol intake (no/yes) | 126 (70.8) / 52 (29.2) | 97 (76.4) / 30 (23.6) | 0.2970 |
| Diabetes (no/yes) | 122 (68.5) / 56 (31.5) | 91 (71.7) / 36 (28.4) | 0.6134 |
| ALBI score | -2.818 (-3.063, -2.546) | -2.574 (-2.870, -2.256) | <0.0001 |
| Maximal tumor size (cm) | 1.6 (1.2, 2.0) | 1.9 (1.4, 2.6) | 0.0002 |
| Number of tumors (single/multiple) | 158 (88.8) / 20 (11.2) | 94 (74.0) / 33 (26.0) | 0.0008 |
| Portal vein invasion (no/yes) | 171 (96.1) / 7 (3.9) | 126 (99.2) / 1 (0.8) | 0.1546 |
| Extrahepatic metastasis (no/yes) | 178 (100) / 0 | 127 (100) / 0 | 1.0000 |
| AFP (ng/mL) | 6.3 (4.0, 15.3) | 17.5 (5.3, 69.1) | <0.0001 |
| AFP-L3 (%) | 0.5 (0.5, 5.5) | 5.3 (0.5, 9.1) | <0.0001 |
| DCP (mAU/mL) | 23 (18, 40) | 32 (17, 76) | 0.0630 |
| Treatment (curative/non-curative) | 148 (83.2) / 30 (16.9) | 103 (81.1) / 24 (18.9) | 0.6512 |

②SVR 後 HCC と HCV 持続感染 HCC の診断後の生存率

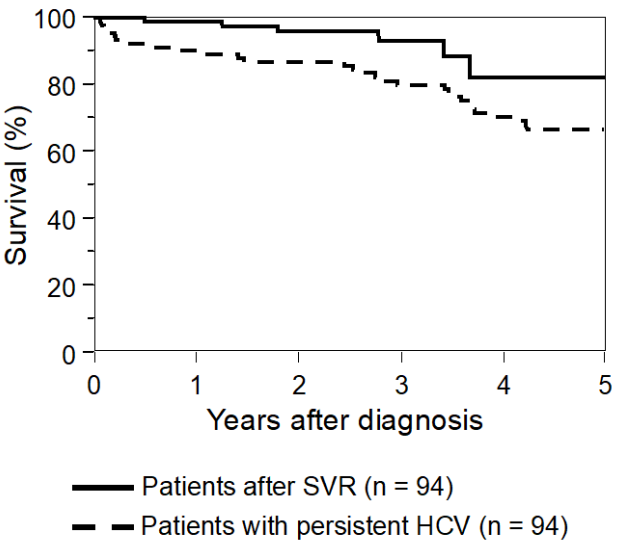
SVR 後 HCC と HCV 持続感染 HCC の初発診断後の生命予後を比較すると、生存率は SVR 後 HCC で有意に高かった（p<0.0001・図 1)。

図1 ：SVR後HCCとHCV持続感染HCCの生存率




ただし、表 1 のごとく、両群間の背景に差があるため、年齢・性別・ALBI score・腫瘍径・腫瘍個数・門脈浸潤を因子として propensity score matching を行なって再度比較したが同様の結果であった（p=0.0174・図 2)。

図2 ：SVR後HCCとHCV持続感染HCCの生存率
（propensity score matching後）




単変量・多変量解析を行うと、多変量解析において、HCC 発生前の SVR の達成は性別・ALBI score・腫瘍径・AFP 値とともに HCC 診断後の生存に有意に関係する因子であり、SVR の達成により初発 HCC 診断後の生存に対する risk ratio は 26.3%に低下した（表 2)。

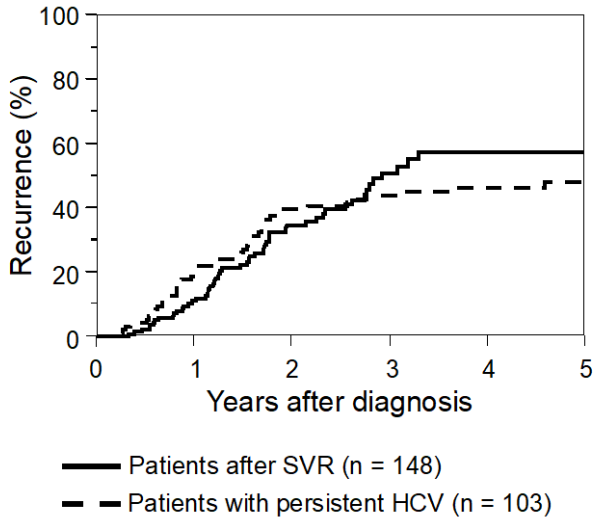
表２：HCC診断後の生存に関与する因子

| Factors | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | p value | Risk ratio (95% CI.) | p value | Risk ratio (95% CI.) |
| Age | per 1.0 year | 0.1415 | 1.023 (0.993-1.057) | | |
| Gender | Male | | Reference | | Reference |
| | Female | 0.0099 | 0.471 (0.245-0.841) | 0.0010 | 0.374 (0.192-0.681) |
| Platelet count | Per 1000 /μL | 0.9646 | 0.999 (0.952-1.045) | | |
| ALBI score | per 1.0 | 0.0008 | 2.298 (1.429-3.606) | 0.0030 | 2.179 (1.311-3.563) |
| MELD score | Per 1.0 | 0.0708 | 1.069 (0.994-1.137) | 0.1635 | 1.061 (0.974-1.138) |
| Maximum tumor size | per 1.0 cm | 0.0008 | 1.529 (1.204-1.892) | 0.0198 | 1.411 (1.058-1.848) |
| Number of tumors | Single | | Reference | | |
| | Multiple | 0.1203 | 1.572 (0.883-2.682) | | |
| Portal vein invasion | Absent | | Reference | | Reference |
| | Present | 0.0387 | 4.469 (1.100-12.686) | 0.4490 | 2.096 (0.257-11.346) |
| AFP | per 1.0 ng/mL | 0.0149 | 1.000 (1.000-1.000) | 0.0108 | 1.000 (1.000-1.000) |
| SVR | Non-SVR | | Reference | | Reference |
| | SVR | <0.0001 | 0.277 (0.134-0.525) | <0.0001 | 0.263 (0.118-0.530) |

③SVR 後 HCC と HCV 持続感染 HCC の根治治療後の再発率

一方、初発 HCC に対して根治治療が施行された症例（SVR 例 148 例・HCV 持続感染例 103 例）でその後の再発率を比較すると、両群間に差は見られなかった（p=0.7484・図 3）。

図3：SVR後HCCとHCV持続感染HCCの根治治療後再発率




そこで両群において、初発 HCC 診断時と再発診断時の間の残存肝機能の変化をみるため ALBI score を比較すると、SVR 例では初発時に比して再発時には ALBI score が有意に低下し（p=0.0191）肝機能が改善していたのに対し、HCV 持続感染例では ALBI score が有意に上昇して（p<0.0001）肝機能の悪化が認められた（図 4）。この結果、再発 HCC に対して再度根治治療が施行できた症例は SVR 例で 56 例中 45 例（80.4%）、HCV 持続感染例で 46 例中 22 例（47.8%）と前者で有意に高かった（p=0.0008）。このため初回再発後の生存率も SVR 例で有意に高かった（p=0.0087・図 5）。

図4：SVR後HCCとHCV持続感染HCCの初発診断時と再発時のALBI score

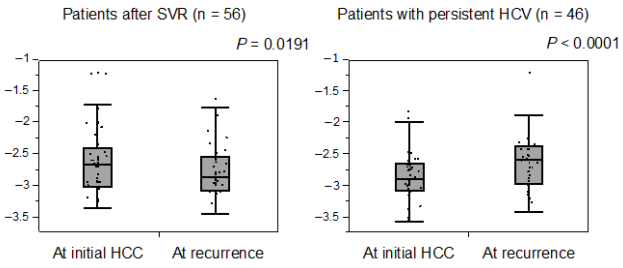
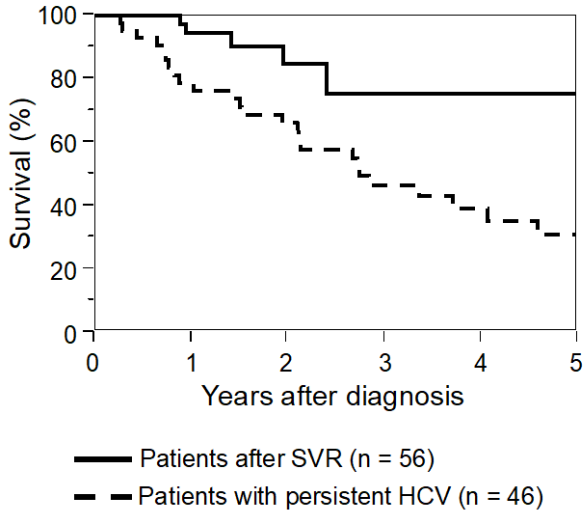



図5：SVR後HCCとHCV持続感染HCCの再発治療後生存率




## D. 結論

上記の検討から、DAAs 治療による SVR 後の初発 HCC について、診断後の生存率は HCV 持続感染例より高いことが明らかとなった。一方で、SVR は HCV 感染症例の発癌率を低下させることが報告されているが、一旦発癌してしまうと完治治療後の再発率を HCV 持続感染例に比して低下させることはできないと考えられた。しかしながら、SVR 症例の残存肝機能は改善していくため、再発に対してもより根治的な治療が可能であることが多く、このことが SVR 後初発 HCC 発生例の生存率を改善させていると考えられた。

## E. 健康危険情報

特記すべきことなし。

## G. 研究発表

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